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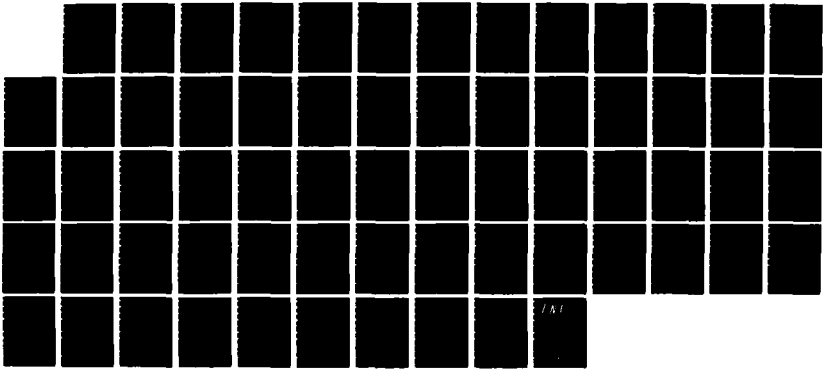

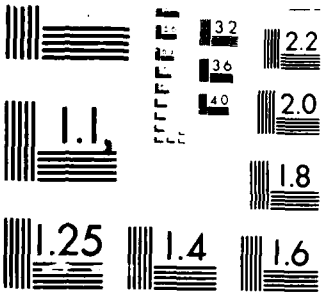

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CHRONIC MAMMALIAN TOXICOLOGICAL EFFECTS OF LAP

Annual Summary Report

By

Ted A. Jorgenson, Ronald J. Spanggord

September 1980

Supported by

U.S. Army Medical Research and Development Command
Fort Detrick, Frederick, Maryland 21701

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Confirmatory LD50 and 14-day range-finding studies on LAP were conducted using the Fischer 344 strain rat in place of the Sprague-Dawley strain rat used in earlier studies. From the results of these studies, dose levels for the chronic phase of the program were established. The overall objective of the chronic phase is to provide a comprehensive definition of the long-term toxicological reactions with respect to possible lesions at the biochemical and cellular levels.

Data from the acute oral studies showed the LD50 of LAP to be 300 mg/kg for male Fischer 344 rats and approximately 280 mg/kg for female Fischer 344 rats. Range-finding results indicated that levels below 0.3% in the diet would be suitable for chronic administration.

Through the first 28 weeks of the chronic study, 43 of 70 male rats in the high-dose LAP group have died. Severe convulsions have been observed in high-dose males and females and in mid-dose males. Females in the high-dose group have become aggressive (fighting).

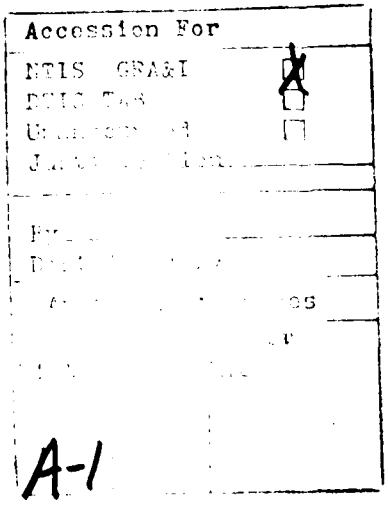
EXECUTIVE SUMMARY

The objectives of this research are to generate comparative acute oral LD50 and 14-day range-finding data on LAP for the Fischer 344 rat relative to the Sprague-Dawley rat and then to conduct a chronic study designed to provide a comprehensive definition of the long-term toxicological reactions of selected biological systems to the individual components of munitions wastewater. The LD50 and range-finding data were used to establish dose levels for the chronic toxicological study.

The acute oral LD50 study examined six dose levels of LAP, using ten males and ten females at each level. The results of this study showed the LD50 to be 300 mg/kg for male Fischer 344 rats and approximately 280 mg/kg for female Fischer 344 rats.

A 14-day range-finding study testing five concentrations in the diet showed reduced food consumption and body weight gains consistently at the 0.5%- and 0.7%-levels for both sexes. Occasionally, food consumption, body weights, gross behavior, and blood parameters were adversely affected at the 0.3%-level. Based on the data from this study, 0.0125, 0.05, and 0.2% were recommended as the dietary levels for the chronic study.

During the first 12 weeks of the chronic study, the high-dose males had severe convulsions, resulting in abrasions about the head and shoulders, followed by death. Consequently, the high-dose level was reduced by 50%. However, the severe convulsions are continuing and 43 of 70 males in the high-dose group have died. Females in the high-dose group have shown increasing aggressive behavior (fighting) toward cage mates. Males in the mid-dose group are showing increasing aggression when being handled as well as in their behavior toward cage mates. Approximately 30% of these males have mild abrasions on face and body (indicative of convulsions).



FOREWORD

In conducting the research described in this report, the investigator(s) adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

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INTRODUCTION

This report describes the work conducted during the first year under Contract No. DAMD 17-79-C-9121.

The overall objective of the proposed research is to provide a comprehensive definition of the long-term toxicological reactions of selected biological systems to individual components of munitions wastewater. These data will constitute a significant part of the overall data base necessary to evaluate the potential hazards of these wastewaters to human health and to define the limits of relative safety. Specific objectives are to identify, verify, and determine the specificity of possible lesions at the biochemical and cellular levels and to further elucidate dose-response relationships.

The studies to be undertaken in this toxicological program are (1) analytical chemistry studies; (2) confirmatory acute oral and 14-day range finding studies; and (3) evaluation of the effect of chronic, dietary administration of LAP in rats. All phases of this project are being performed in accordance with the FDA Good Laboratory Practices.

EXPERIMENTAL

General

The contract was signed on 1 September 1979. Compound acquisition began in September 1979 and the compounds, 2,4,6-trinitrotoluene (TNT) and 1,3,5-trinitrohexahydro-1,3,5-triazine (RDX), were received in November 1979.

AMRDC personnel visited the SRI facilities and engaged in program discussions on 10 October 1979 and 9-10 January, 5 May, and 22-23 August 1980. All discussions and reviews proceeded as planned, and the program is proceeding as scheduled.

Analytical Chemistry

Peroxide Levels in Corn Oil

Each batch of corn oil, used as a vehicle in this program, is assayed for peroxide. These determinations are conducted by iodometric titration.[1] To date there have been two shipments of four 5-gallon cans each. The first shipment contained 0.577 meq peroxides/kg of corn oil and the second shipment contained 4.68 meq peroxides/kg of corn oil.

Pesticide Residues in Stock Feed

Purina Certified Rodent Chow 5002 and Rodent Laboratory Chow 5001 were analyzed for the pesticides listed in Table 1; the list includes both organochlorine and organophosphate pesticides.

Feed samples were extracted and cleaned up according to official AOAC methods.[2] The extracts were analyzed for chlorinated organic pesticides using glass capillary gas chromatography (GC) and electron capture (EC) detection under the following conditions:

Varian 3740 GC, EC detector 300°C, injector 25°C.
Column: SP-2100 Scot, 220°C isothermal, N_2 10 psi, 0.8 ml/min
Attenuation 4 Range 10^{-12}

Analyses for organohposphate pesticides were performed by packed column GC, using alkali-flame ionization detection under the following conditions:

HP 5730A, N-P detector 300°C, injector 250°C.
Column: 10% DC-200, 6' 220° isothermal, Range 1, vols: ~ 19
H_3-3 ml/min, Air-50 ml/min, N_2-30 ml/min.

Gas chromatographic profiles of the certified and noncertified diets appear in Figures 1 and 2, respectively. Peaks were identified tentatively by retention time and peak enhancement. Quantitative estimates of identified components appear in Table 2, and GC/mass spectroscopic confirmation is in progress. The results indicate that there is no advantage or disadvantage to using certified diets in animal studies. Although coelution of feed components may interfere with the quantitation of pesticide components (making the values higher than the actual values), the noncertified diet does not contain contaminent levels greater than those stated for the certified diet.

The United States Army Medical Research and Development Command specified the use of Purina Certified Rodent Chow 5002 throughout this program.

Pesticide Residues in Water

The water to be used in the animal facility during this program was analyzed for the pesticides listed in Table 1. One-liter samples were extracted with diethyl ether, concentrated in a Kurdema-Danish apparatus, and analyzed by glass capillary GC using EC detection. None of the pesticides was identified in amounts above 0.1 ppb. A microbiologic screen produced no colonies.

Purity and Stability of TNT/RDX

Both TNT and RDX were characterized and found to be more than 99% pure. Calculated quantities of TNT and RDX in a ratio of 1.6:1 (LAP) were dissolved in acetone and added to a predetermined volume of corn oil. The acetone was then removed by roto-evaporation. Vehicle controls were corn oil with acetone added and removed in the same manner as for the LAP samples. Stability studies using this method showed that diets mixed once every two weeks were stable.

Homogeneity Study

The homogeneity of the diet mixes was determined. Six dose levels were examined, with the following results:

Dose Level (ppm)	Area of Mixer Sampled	LAP Found (ppm)	Percent Variance
2500	Top	2474	- 1.0
	Middle	2582	+ 3.3
	Bottom	2358	- 5.7
2200	Top	2124	- 3.4
	Middle	2116	- 3.8
	Bottom	2094	- 4.8

Dose Level (ppm)	Area of Mixer Sampled	LAP Found (ppm)	Percent Variance
585	Top	572	- 2.3
	Middle	529	- 9.6
	Bottom	544	- 7.0
540	Top	465	-13.9
	Middle	466	-13.7
	Bottom	480	-11.0
145	Top	134	- 7.8
	Middle	131	- 9.9
	Bottom	124	-14.4
132	Top	110	-16.4
	Middle	110	-16.4
	Bottom	109	-17.4

As shown above, we were obtaining a uniform distribution of test material throughout the diet. We continued to examine recovery techniques and mixing times.

Diet Analyses

Diets prepared during the first 13 weeks and one mix in each quarter thereafter were analyzed for TNT and RDX. Samples were saved from each diet mix, regardless of whether it was analyzed. The analytical results of the diet preparations analyzed to date are presented in Table 3.

The evaluation of the estrogen and heavy metal content in Purina Certified Diet was begun.

Toxicology

The specific individual mammalian protocols for the acute, 14-day range-finding, and chronic studies are on file with the Project Officer and will not be duplicated in this report.

Acute LD50 Confirmation

In previous acute studies conducted on LAP (TNT/RDX), using the Sprague-Dawley rat, LD50 values ranged from approximately 300 ppm to greater than 600 ppm. The acute LD50 study conducted for this program was designed to account for the manner in which the TNT and RDX were incorporated into the corn oil and to investigate the response in the Fischer 344 rat. Ten males and ten females were randomly assigned to a vehicle control and six compound treatment levels. Controls received a corn oil-acetone mixture. The six compound (LAP) groups received one of the following levels: 150, 300, 450, 600, 750, or 900 mg/kg.

All animals received a single oral dose by gavage. The following mortality data were recorded over the 14-day observation period.

Dose Level (mg/kg)	Males		Females	
	Number Treated	Number Dead	Number Treated	Number Dead
900	10	10	10	10
750	10	10	10	10
600	10	10	10	10
450	10	8	10	9
300	10	5	10	4
150	10	2	10	4

Initially the data were analyzed using one or more of the statistical procedures listed on page 13 of the Mammalian Toxicology Protocol--Acute Mammalian Toxicological Effects of LAP. The results of these analyses showed the LD50 of LAP to be 300 mg/kg for male Fischer 344 rats and 280 mg/kg for female Fischer 344 rats. Since these data were comparable to those obtained in previous studies using Sprague-Dawley rats, we were requested to proceed with the program using the Fischer 344 rat. In a further evaluation conducted using a computer-generated statistical program, the results obtained were in good agreement with those previously determined for the male Fischer 344 rat. For the females, however, it was extremely difficult to accurately determine the LD50. Originally we used a simple method of estimating 50% end-points.[3] Using linear interpolation on the log doses, a point estimate for the LD50 is 325.3 mg/kg. Since this was consistent with previous values, no further acute work was conducted. The computer-generated, acute data are presented in Attachment A to this report.

14-Day Range-Finding Study

The purpose of this study was to determine the cumulative toxicity response to LAP in the Fischer 344 rat over 14 days and compare the data with previously collected 90-day data using Sprague-Dawley rats. This comparison permitted us to evaluate the strain differences as well as the effects of the treatment in support of dosage selection for the chronic study. Ten males and ten females were randomly assigned to each of six experimental groups (vehicle control, 0.05, 0.1, 0.3, 0.5, and 0.7%). Diets were prepared (corn oil/acetone, or LAP (TNT/RDX)/acetone/corn oil) as described earlier. Body weights and food consumption were recorded weekly; the animals being observed daily for 14 days. Hematology and clinical chemistry determinations were conducted on the survivors at termination of the study.

Tables 4 through 11 provide the computer-generated data for body weights and food consumption from the 14-day study. Tables 4 and 5 summarize the body weight data for males and females, respectively.

The males were significantly lighter than controls beginning with the 0.1% level while the females were significantly different beginning with the 0.3% level. Differences in body weights after one and two weeks are presented for males and females in Tables 6 and 7, respectively. The effects are more dramatic in these tables, with significant differences appearing one dose level below the affected levels in Tables 4 and 5. Also apparent in Tables 6 and 7 are the significant recoveries toward the control values from Week 1 to Week 2.

Food consumption data are summarized in Tables 8 through 11. Consumption based on grams of food consumed per kilogram of body weight per day is shown in Table 8 for male rats and in Table 9 for female rats. Consumption based on grams of food consumped per day is presented in Tables 10 (males) and 11 (females). The results show a definite dose-related response during Week 1, with indications of acclimation (recovery toward control values) during Week 2.

The hematology data for both males and females are summarized in Table 12. Table 13 summarizes the serum clinical chemistry data for both males and females. Various hematology and clinical chemistry parameters show dose-related fluctuations from the control values. In a study of this duration, using so few animals and using young growing animals, it is difficult to accurately evaluate the indiviudal variations in effects. Although fluctuations were observed in this study, we cannot separate effects caused by the compound from effects due to reduced food consumption and/or naturally occurring changes because of the age of the animals. We can, however, state that the combination of effects show that the 0.7%, 0.5%, and occasionally the 0.3% dose levels are not suitable for longer-term testing and thus represent definitive effect levels in this study.

The terminal necropsy performed on these animals did not produce a target organ response, nor did any critical lesions occur that required further investigation. Therefore, no histopathology was conducted on the tissues collected from these animals.

Based on the data collected from this study, we recommended that 0.0125, 0.05, and 0.2% be the dose levels incorporated into the diets for the chronic study.

Chronic Study

The purpose of this phase of the program is to provide a comprehensive definition of the long-term toxicological reactions of selected biological systems to LAP.

The rats for the chronic phase were received on 17 January 1980 and placed in quarantine. During quarantine, we experienced difficulties with the automatic watering system and our new stainless steel animal racks. We discovered that the flushing of the watering system had not been thorough enough following the installation of the plastic pipe.

Hence, vapors from curing of the glue built up in the pipe. When the rack was brought into the system, the toxicity of the vapor/water mixture caused some of the animals to get sick and die. We sacrificed the remaining animals and placed a replacement order immediately. The replacement animals were delivered on 31 January 1980. Before this second shipment of animals arrived, all new animal racks and watering systems were thoroughly flushed and the purity of the water was verified by our Analytical Chemistry Department.

The chronic study was initiated on 14 February 1980. The dietary preparation and exposure regimen was changed from a constant 0.0125, 0.05, and 0.2% in the diet to 12.5, 50, and 200 mg/kg/day in the diet, adjusted every two weeks.

The initial eye examination was normal for all animals. All were randomly allocated to the study according to the procedures delineated in the Mammalian Toxicology Protocol for the chronic study, which is on file with the Project Officer.

Data on food consumption and body weight through the first 24 weeks of the chronic study are summarized in Tables 14 through 21. Tables 14 and 15 show food consumption based on grams per kilogram of body weight per day and Tables 16 and 17 show consumption based on grams per rat per day. Even-numbered tables provide data for male rats and odd-numbered tables provide data for female rats. Consumption of the mid- and high-dose males was generally significantly less than that for controls during the first 16 weeks on test (based on grams consumed per rat per day), but was generally consistent with control levels during Weeks 17 to 24. Females showed a similar pattern through the first 12 weeks, showed a recovery in consumption consistent with control values during Weeks 13 to 21, and then a significant increase in consumption above control values for the high-dose level during Weeks 22 to 24. The observed recoveries can be accounted for in three ways. First, for the high dose, we reduced the concentration from 200 mg/kg/day to 100 mg/kg/day starting with Week 13 because of the deaths and convulsions observed in the high-dose males during Weeks 10 to 12. Next, we believe that the animals had finally adapted to the concentrations of LAP present in their diets and/or they reached a plateau in consumption consistent with maintaining their body weight, including occasional slow rates of growth.

Tables 18 and 19 present average body weights and Tables 20 and 21 show differences in body weights, or body weight gain. A review of the statistical evaluation for Weeks 1 through 24 has shown significant differences occurring in all groups for both sexes. The data are so uniform (thus producing extremely low and consistent standard errors) that, statistically, very small variations are significant. Biologically, however, the data to date do not indicate that there is an effect at the low dose (12.5 mg/kg/day).

Figures 3 and 4 provide an indication of any significant trends relative to biological effects. For instance, the mid-dose male group

in Figure 3 is showing a steady increase in the deviation from the control group, thus indicating a change taking place in the males at that level.

We have consistently observed severe convulsions in the high-dose males. Convulsions have become more apparent in females over the last 8 weeks, but are less severe than in the males. Females have also shown aggressive behavior (fighting, generally associated with males) toward cage mates.

Through the first 28 weeks of test (to 28 August 1980), 43 of 70 males died or reached a state of health that required sacrifice. The tissues from these animals that died have been submitted for histopathology. The results of the histological evaluation will be reported in the appropriate monthly report and in the annual report for Year 2.

DISCUSSION AND CONCLUSIONS

The acute oral LD50 study produced values in male and female Fischer 344 rats comparable to those found previously in Sprague-Dawley rats. Within the scope of this program, this study was considered adequate to proceed with the contract using the Fischer 344 rat.

A 14-day range-finding study showed levels of toxicity below previously suggested treatment for the chronic study. As a result of this range-finding study, 0.0125, 0.05, and 0.2% in the diet were recommended for the chronic study.

To date the chronic study has been on test for 28 weeks. Just prior to the start of the chronic study the treatment levels were changed from those stated above to 12.5, 50, and 200 mg/kg/day in the diet adjusted once every two weeks according to body weight and food consumption averages. Serious effects on the high dose males were observed during the first 12 weeks that prompted a reduction of that level from 200 mg/kg/day to 100 mg/kg/day. It is unlikely that the high-dose males will survive to the end of this 2-year chronic study. Based on the data presented in this report we conclude that the 12.5 gm/kg/day level remains a no-effect level, that the 50 mg/kg/day level presently represents a mild to moderate effect level, and that the 100 mg/kg/day level represents a definitive effect level.

REFERENCES

1. Official Methods of Analysis of the Official Association of Analytical Chemists, 11th edition, 1970, p. 445.

2. Ibid., p. 481.

3. L. J. Reed and H. Muench. Am. J. Hyg. 27, 493-497 (1938).

ACKNOWLEDGMENTS

This program is being conducted in the Life Sciences Division under the direction of Dr. David C. L. Jones, Director, Toxicology Laboratory. The experimental work in toxicology is being directed by Ted A. Jorgenson, Director, Mammalian Toxicology Department. The chemical and analytical work is being directed by Dr. Ronald J. Spanggord, Director, Bio-Analytical Chemistry Program. Dr. Daniel P. Sasmore, Director of Pathology, is responsible for the histopathological preparations and microscopic examination of tissues. Dr. Harold S. Javitz, Statistician, and Larry Walter developed and processed the computer work. Drs. Jones, Spanggord, Javitz, and Sasmore, along with Mr. Jorgenson, are responsible for the analysis of the experimental data. Technical assistance and support are provided by chemists in the Bio-Analytical Chemistry Program (Rodney Keck, Daniel Combs, and Mike Regalia) and the technical staff of the Mammalian Toxicology Department (Peter Gribling, Juan Dulude, Sandra Phillips, Janice Brown, Loreli Brown, John Wharton, Steve Halperin, Mark Gilbert, and Janet Cortopassi). Carol Rushbrook, Toxicologist, provides scheduling and coordination.

During the past year Kathleen Dulude, Ernestine Seay, and Robert Harding provided some assistance in this program. Kathleen Dulude has transferred to another department in the Toxicology Laboratory, Ernestine Seay has returned to Animal Care Services for reassignment, and Robert Harding resigned.

Table 1

PESTICIDES ASSAYED FOR IN PURINA CHOWS

Chlorinated Pesticides	Organophosphate Pesticides
Heptachlor	Phorate
Aldrin	Diazinon
Heptachlor epoxide	Disulfoton
Chlordane	Methyl parathion
DDE	Malathion
Dieldrin	Parathion
Endrin	Ethion

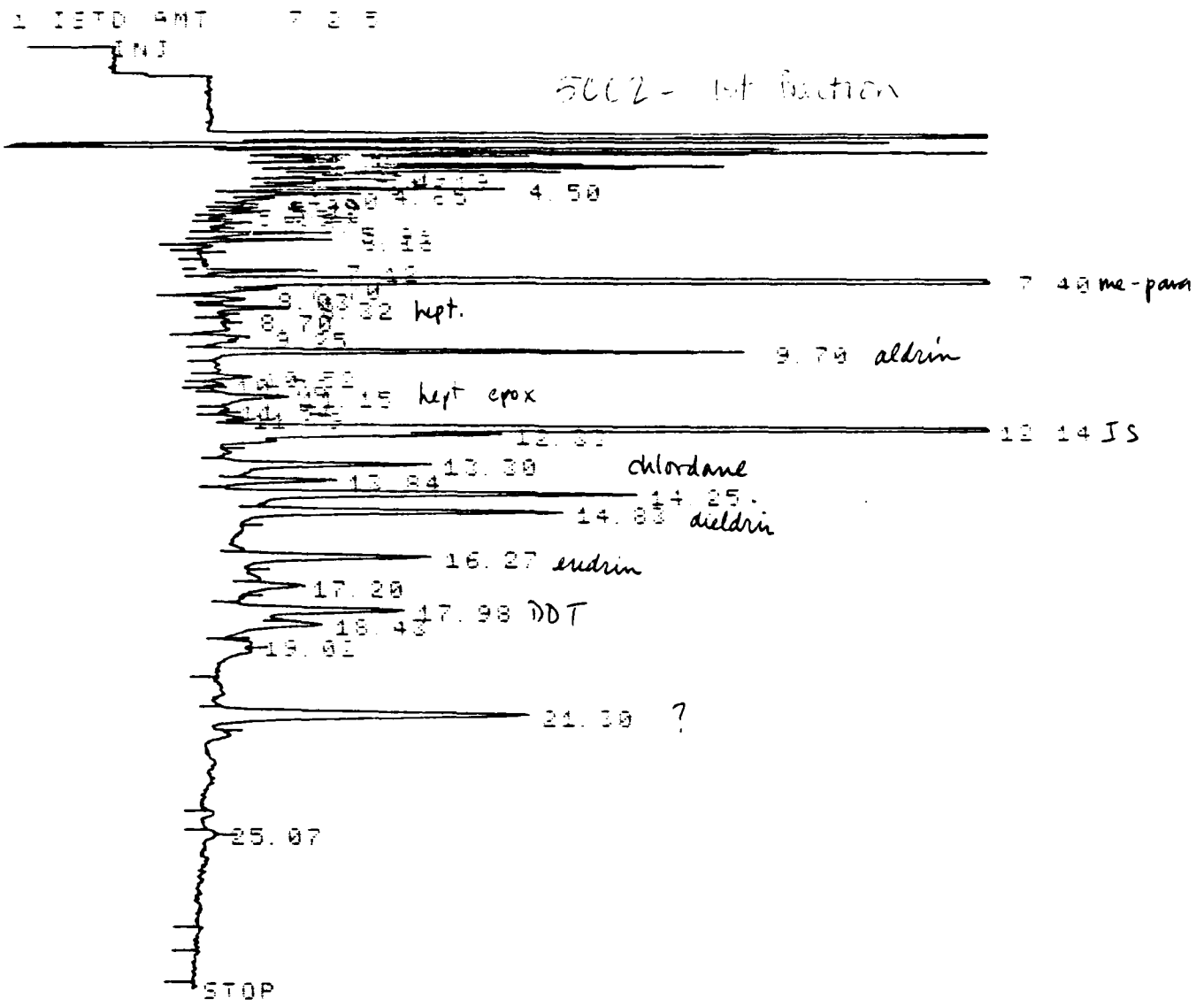

Figure 1. Chromatographic Profile of Pesticide Residues in Certified Diet

RT	TYPE	AREA	ISTD ID#	AMT
7.40	M	39973		
8.70	M	42231	2	.027 82
12.14		105512	1	
13.04	M	8572		
13.30		21154	5	.449 4
13.84	M	11107		
14.15	M	44899	3	.164 1
14.83	M	14683	7	.021 83
16.27		20112	8	.017 51
17.98		21557	9	2.011
18.43	M	17327		
21.30		45403		

TOTAL 2.651 86

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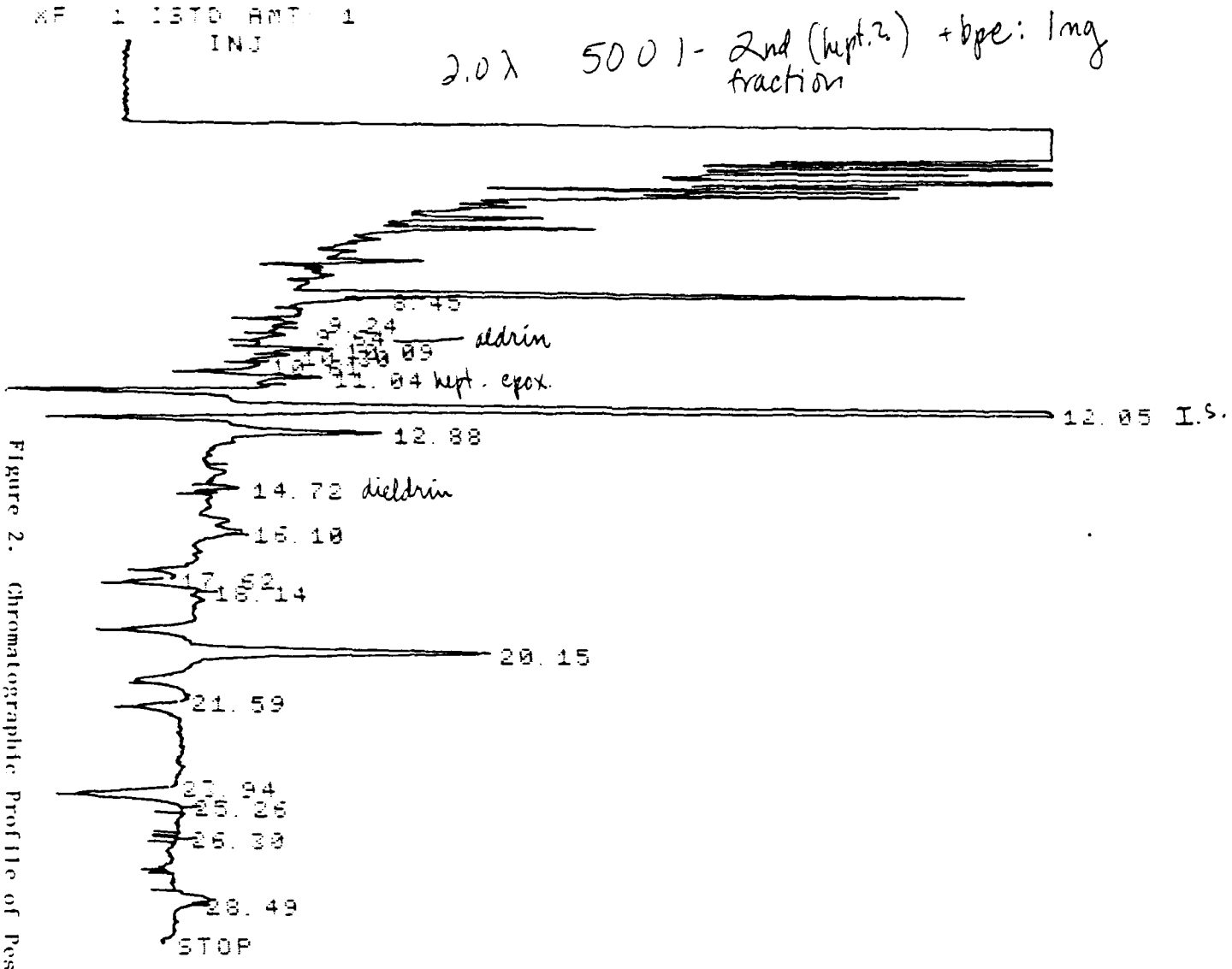


Figure 2. Chromatographic Profile of Pesticide Residues in Non-Certified Diet

	RT	TYPE	AREA	ISTD ID#	AMT
	8.45	M	492		
	9.24		291		
	9.54		150	3	000 501 9
	10.09		526		
	10.30	M	386		
	10.61		510		
	11.04	M	893	4	060 48
	12.05		30060	1	
	12.88	M	8047		
	13.44		242	7	000 001 5
	13.70		425	8	001 82
	13.93		562		
	14.45	M	205		
	14.72		11193		
	15.33	M	3457		
	16.14	M	14776		
	16.50	M	321		
	17.43		510		

TOTAL 061 600 4

F 1 ISTD AMT 1.

Table 2

QUANTITATIVE ESTIMATE OF PESTICIDES IDENTIFIED IN PURINA CHOWS

Chemical	Rodent Laboratory Chow 5001	Certified Rodent Chow 5002	Max. for 5002 Feed as Certified (ppm)
Heptachlor	0.0045 ppm	0.077 ppm	0.05
Aldrin	0.001	not detected	0.05
Heptachlor epoxide	not detected	0.006	0.05
Chlordane	not detected	0.021	0.05
DDE	not detected	0.015	0.15
Dieldrin	0.001	0.001	0.05
Endrin	not detected	0.001	0.05
Phorate	not detected	0.004	0.5
Diazinon	0.001	0.001	0.5
Disulfoton	not detected	0.003	0.5
Methyl parathion	0.002	0.007	0.5
Malathion	0.072	0.110	0.5
Parathion	0.003	0.013	0.5
Ethion	not detected	not detected	0.5

Table 3

CHRONIC FEEDING STUDY OF LAP:
ANALYSES OF DIET PREPARATIONS

Week of Study	LAP Concentration (ppm)			Concentration (mg/l)		TNT/RDX Ratio
	Intended	Actual	Percent Change from Intended	TNT	RDX	
1 and 2	125	110	-12.0	18.0	9.4	1.91
	500	476	- 3.7	75.3	43.8	1.72
	2000	1844	- 7.8	288.0	173.0	1.66
3 and 4	132	110	-16.9	17.5	9.5	1.83
	145	130	-10.7	20.1	11.5	1.75
	540	471	-12.9	72.9	44.0	1.66
	585	548	- 6.3	85.9	52.8	1.63
	2200	2111	- 4.0	319.7	211.3	1.52
	2500	2471	- 1.1	361.0	245.9	1.47
5 and 6	146	129	-11.9	20.0	11.6	1.72
	169	148	-12.2	23.4	13.8	1.70
	595	566	- 4.9	86.9	54.1	1.61
	685	643	- 6.1	96.7	60.1	1.61
	2600	2609	+ 0.4	379.1	270.0	1.40
	2700	2574	- 4.7	372.7	252.5	1.48
7 and 8	165	154	- 6.7	23.3	15.1	1.55
	200	185	- 7.4	27.7	17.5	1.58
	775	757	- 2.4	115.6	74.3	1.56
	800	768	- 4.0	121.1	72.2	1.68
	3200	3089	- 3.5	443.6	305.9	1.45
9 and 10	188	180	- 4.0	28.5	18.5	1.54
	220	208	- 5.5	32.1	21.1	1.53
	800	814	+ 1.7	121.9	81.5	1.50
	875	897	+ 2.5	138.8	89.4	1.55
	3200	2996	- 6.4	452.8	293.1	1.55
11 and 12	181	166	- 8.5	25.8	15.6	1.65
	235	222	- 5.7	34.9	21.1	1.66
	840	797	- 5.1	124.8	77.0	1.62
	950	878	- 7.6	133.1	86.8	1.53
	3200	3020	- 5.6	462.6	296.4	1.56
	3500	3279	- 6.3	528.8	292.6	1.81
13 and 14	220	221	+ 0.6	35.4	21.7	1.63
	255	233	- 8.8	37.4	22.8	1.64
	900	830	- 7.8	122.0	77.7	1.57
	1035	974	- 5.9	152.9	92.1	1.66
	1670	1634	- 2.2	236.6	149.3	1.59
	1800	1715	- 4.7	279.0	165.2	1.69

Table 3 (continued)

Week of Study	LAP Concentration (ppm)			Concentration (mg/l)		TNT/RDX Ratio
	Intended	Actual	Percent Change from Intended	TNT	RDX	
23 and 24	245	228	- 6.78	26.2	21.3	1.70
	280	248	-11.50	38.1	23.0	1.66
	975	951	- 2.45	158.0	88.3	1.79
	1050	1004	- 4.38	149.9	90.4	1.66
	1750	1570	-10.30	239.1	140.9	1.70
	1875	1788	- 4.64	292.4	167.2	1.75

TABLE 4

EFFECTS OF LAP ON BODY WEIGHTS (G)
OF MALE RATS DURING 2 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS									
		0.05	T R	0.1	T R	0.3	T R	0.5	T R	0.7	T R
INITIAL	75.60 (3.22)	79.20 (2.34)		77.90 (3.87)		79.10 (3.53)		77.00 (3.49)		77.90 (3.27)	
WEEK 1	105.70 (3.29)	101.30 (2.08)		93.60 (4.09)	*	76.30 (3.83)	+ A	59.44 (2.65)	+ C	52.33 (7.84)	+ C
WEEK 2	142.60 (3.63)	135.20 (5.59)		124.90 (4.41)	+	92.80 (3.96)	+ B	65.14 (3.47)	+ C	70.00 (0.00)	+ B

ENTRIES ARE MEANS WITH STANDARD ERRORS IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
CONFIDENCE INTERVAL IS HIGHER OR LOWER THAN MEAN BY AT LEAST : 10 PERCENT - A, 20 PERCENT - B,
35 PERCENT - C OR 50 PERCENT - D

TABLE 5

EFFECTS OF LAP ON BODY WEIGHTS (G)
OF FEMALE RATS DURING 2 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS									
		0.05	T R	0.1	T R	0.3	T R	0.5	T R	0.7	T R
INITIAL	68.00 (3.14)	70.80 (3.01)		70.80 (2.75)		68.50 (3.76)		69.00 (2.82)		68.40 (3.50)	
WEEK 1	85.30 (3.57)	86.50 (3.56)		78.80 (3.86)		63.80 (3.60)	+ A	54.90 (1.23)	+ B	57.00 (0.00)	+ B
WEEK 2	106.50 (3.71)	108.70 (4.10)		97.90 (5.00)		74.40 (3.70)	+ B	61.30 (1.35)	+ C		

ENTRIES ARE MEANS WITH STANDARD ERRORS IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
CONFIDENCE INTERVAL IS HIGHER OR LOWER THAN MEAN BY AT LEAST : 10 PERCENT - A, 20 PERCENT - B,
35 PERCENT - C OR 50 PERCENT - D

TABLE 6

EFFECTS OF LAP ON DIFFERENCES IN BODY WEIGHTS (G)
OF MALE RATS DURING 2 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS									
		0.05	T R	0.1	T R	0.3	T R	0.5	T R	0.7	T R
WEEK 1	30.10 (1.05)	22.10 (2.82)	*	15.70 (1.44)	+ C	-2.80 (1.53)	+ D	-16.89 (1.97)	+ D	-25.67 (6.17)	* D
WEEK 2	36.90 (1.02)	33.90 (3.99)		31.30 (.883)	+	16.50 (1.19)	+ C	5.43 (3.04)	+ D	5.00 (0.00)	+ D

ENTRIES ARE MEANS WITH STANDARD ERRORS IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
CONFIDENCE INTERVAL IS HIGHER OR LOWER THAN MEAN BY AT LEAST : 10 PERCENT - A, 20 PERCENT - B,
35 PERCENT - C OR 50 PERCENT - D

TABLE 7

EFFECTS OF LAP ON DIFFERENCES IN BODY WEIGHTS (G)
OF FEMALE RATS DURING 2 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS									
		0.05	T R	0.1	T R	0.3	T R	0.5	T R	0.7	T R
WEEK 1	17.30 (1.65)	15.70 (1.24)		8.00 (2.29)	+ B	-4.70 (1.28)	+ D	-14.10 (1.92)	+ D	-24.00 (7.00)	+ D
WEEK 2	21.20 (.998)	22.20 (.964)		19.10 (2.12)		10.60 (.991)	+ C	6.40 (.872)	+ D		

ENTRIES ARE MEANS WITH STANDARD ERRORS IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
CONFIDENCE INTERVAL IS HIGHER OR LOWER THAN MEAN BY AT LEAST : 10 PERCENT - A, 20 PERCENT - B,
35 PERCENT - C OR 50 PERCENT - D

TABLE 8

EFFECTS OF LAP ON FOOD CONSUMPTION (G/KG (BODY WT)-DAY)
OF MALE RATS DURING 2 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS									
		0.05	W	0.1	W	0.3	W	0.5	W	0.7	W
WEEK 1	113.2 (.965)	102.8 (1.19)		95.7 (1.48)	*	66.9 (1.30)	*	46.9 (4.90)	*	22.2 (2.40)	*
WEEK 2	94.1 (.941)	90.2 (.747)		90.9 (.249)		86.8 (.302)		76.7 (4.08)	*	76.8 (0.00)	*

ENTRIES ARE CAGE MEANS WITH STANDARD ERRORS IN PARENTHESES
W = WILLIAMS TEST OF LOWEST SIGNIFICANT CONTROL-TREATMENT COMPARISON
* CONFIDENCE LEVEL = .95

TABLE 9

EFFECTS OF LAP ON FOOD CONSUMPTION (G/KG (BODY WT)-DAY)
OF FEMALE RATS DURING 2 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS									
		0.05	W	0.1	W	0.3	W	0.5	W	0.7	W
WEEK 1	100.8 (1.60)	96.9 (1.81)		87.8 (2.34)		61.4 (6.46)	*	44.9 (8.21)	*	10.8 (9.61)	*
WEEK 2	89.5 (.492)	85.0 (.110)		86.8 (2.40)		84.5 (.173)		79.5 (1.97)	*		

ENTRIES ARE CAGE MEANS WITH STANDARD ERRORS IN PARENTHESES
W = WILLIAMS TEST OF LOWEST SIGNIFICANT CONTROL-TREATMENT COMPARISON
* CONFIDENCE LEVEL = .95

TABLE 10

EFFECTS OF LAP ON FOOD CONSUMPTION (GRAMS/DAY)
OF MALE RATS DURING 2 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS									
		0.05	W	0.1	W	0.3	W	0.5	W	0.7	W
WEEK 1	12.0 (.271)	10.4 (.357)	*	9.0 (.014)	*	5.1 (.014)	*	2.8 (.414)	*	1.2 (.099)	*
WEEK 2	13.4 (.186)	12.2 (.714)		11.4 (.186)		8.1 (.371)	*	5.0 (.166)	*	5.4 (0.00)	*

ENTRIES ARE CAGE MEANS WITH STANDARD ERRORS IN PARENTHESES
W - WILLIAMS TEST OF LOWEST SIGNIFICANT CONTROL-TREATMENT COMPARISON
* - CONFIDENCE LEVEL = 95

TABLE 11

EFFECTS OF LAP ON FOOD CONSUMPTION (GRAMS/DAY)
OF FEMALE RATS DURING 2 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 0.05	W	0.1	W	0.3	W	0.5	W	0.7	W
WEEK 1	8.6 (.429)	8.4 (.186)		6.9 (.114)		3.9 (.400)	*	2.5 (.500)	*	.6 (.548)	*
WEEK 2	9.5 (.243)	9.2 (.071)		8.5 (.086)	*	6.3 (.114)	*	4.9 (.129)	*		

ENTRIES ARE CAGE MEANS WITH STANDARD ERRORS IN PARENTHESES
W = WILLIAMS TEST OF LOWEST SIGNIFICANT CONTROL-TREATMENT COMPARISON
* CONFIDENCE LEVEL = 95

Table 12

EFFECTS OF LAP ON HEMATOLOGY OF MALE AND FEMALE RATS
FOLLOWING TWO WEEKS OF TREATMENT

Treatment Group	WBC x10[3]	RBC x10[6]	Hgb gm %	Hct %	MCV μ^3	MCH µµg	MCHC %	Differential Count (%) PMN	Band	Lymph	Mono	Eosino	Baso
Males													
Control	7.2 (7)*	7.22 (9)	13.6 (9)	41.3 (9)	56 (9)	18.7 (9)	32.9 (9)	16	0	83	1.5	0.1	0
0.05%	6.3	7.27	13.3	40.2	54	18.1	33.1	23	0	75	2.3	0.3	0
0.1%	6.5	7.31	13.1	39.8	53	17.7	32.9	24	0	76	0.4	0.1	0
0.3%	7.4	7.11	12.4	38.0	52	17.3	32.8	30	0.2	68	1.9	0.3	0
0.5%	3.5 (5)	6.21 (7)	11.6 (7)	33.9 (7)	53 (7)	18.4 (7)	34.2 (7)	39 (7)	0.6 (7)	58 (7)	2.4 (7)	0.3 (7)	0 (7)
0.7%	6.8 (1)	5.58 (1)	11.2 (1)	32.0 (1)	55 (1)	19.7 (1)	34.8 (1)	41 (1)	0 (1)	58 (1)	1 (1)	0 (1)	0 (1)
Females													
Control	5.5	7.33	1.7	40.5	55	18.5	33.6	20	0.1	77	2.5	0.6	0
0.05%	5.0	7.39	13.6	41.4	55	18.2	32.6	20	0	80	2.4	0	0
0.1%	5.4 (9)	7.30 (9)	13.2 (9)	40.4 (9)	54 (9)	17.9 (9)	32.6 (9)	26	0.1	73	1.1	0.6	0
0.3%	4.8	7.47	12.8	39.7	53	17.2	32.1	40	0	58	2.0	0.7	0
0.5%	10.4 (8)	6.06 (8)	13.0 (8)	39.0 (8)	61 (8)	20.5 (8)	33.1 (8)	33	0.2	61	1.8	0.8	0
0.7%	All females died												

* ( ) Number of rats in sample if different from 10.

Table 13

EFFECTS OF EAP ON SERUM CLINICAL CHEMISTRIES
OF MALE AND FEMALE RATS FOLLOWING TWO WEEKS OF TREATMENT

Parameter Examined	Treatment Group - Males						Treatment Group - Females*				
	Control	0.05%	0.1%	0.3%	0.5% (7)†	0.7% (1)	Control	0.05%	0.1%	0.3%	0.5% (7)
Glucose mg %	153	157	142	106	29	14	107	110	91	42	20
BUN mg %	14	14	13	11	4	5	12	11	9	7	5
Creatinine mg %	0.5	0.5	0.4	0.4	0.2	0.2	0.4	0.4	0.3	0.2	0.2
Uric acid mg %	2.3	2.4	2.4	2.1	0.6	0.7	2.1	2.2	2.0	0.9	1.0
Na^+ meq/L	146	146	147	147	151	150	148	148	149	150	152
K^+ meq/l	5.3	5.5	5.5	3.7	1.6	1.5	3.9	4.2	3.7	2.6	2.2
CO_2 meq/L	16	17	17	10	2	4	11	12	10	5	1.7
Cl meq/L	109	109	111	124	145	145	122	119	124	135	142
Calcium mg %	9.0	9.0	8.8	6.2	2.4	2.6	6.8	7.4	6.2	3.8	2.4
Phosphorus mg %	8.7	7.6	8.2	5.7	2.6	2.1	6.0	7.1	5.5	4.4	3.5
Balance ($Na-[Cl + CO_2]$)	20	19	18	13	3.3	1	14	18	15	11	8
Cholesterol mg %	57	62	65	53	27	38	52	59	54	41	33
Triglycerides mg %	91	49	65	43	25	21	24	16	12	9	17
Total Bilirubin mg %	0.07	0.08	0.1	0.08	0.08	0.1	0.05	0.09	0.07	0.05	0.1
SGOT mU/ml	267	187	242	116	88	51	318	239	222	184	240
SGPT mU/ml	110	74	93	37	19	10	105	89	83	47	53
LDH mU/ml	1529	925	1167	672	325	267	1729	1486	1183	827	846
Alkaline Phosphatase mU/ml	824	622	550	335	118	117	393	431	346	192	128
Total Iron mcg %	217	293	196	191	77	88	202	182	162	116	70
Total Protein gm %	4.8	4.9	4.8	3.7	1.5	1.7	3.8	4.4	3.6	2.3	1.8
Albumin gm %	2.4	2.4	2.4	1.8	0.7	0.8	1.9	2.2	1.8	1.1	0.8
Globulin gm %	2.4	2.5	2.4	1.9	0.9	0.9	1.9	2.2	1.8	1.2	0.9
A/G	1.0	1.0	1.0	0.9	1.0	0.9	1.0	1.0	0.9	1.0	0.9

* All females died at the 0.7% level.
† ( ) Number of rats in sample if different from 10.

TABLE 14

EFFECTS OF LAP ON FOOD CONSUMPTION (G/KG (BODY WT)-DAY) OF MALE RATS

DEPENDENT VARIABLE	TREATMENT GROUPS					
	CONTROL	12.5 MG/KG	W	50 MG/KG	W	200 MG/KG	W
WEEK 1	85.7 ± .726 (15)	85.6 ± 1.36 (14)		80.8 ± 1.20 (14)		51.4 ± 1.31 (14)	*
WEEK 2	75.9 ± .662 (15)	73.3 ± 1.31 (14)		73.4 ± 2.14 (14)		80.1 ± 1.70 (14)	
WEEK 3	74.9 ± .739 (15)	77.0 ± 1.13 (14)		76.0 ± .644 (14)		75.1 ± .679 (14)	
WEEK 4	76.7 ± 1.66 (15)	73.4 ± 1.18 (14)		76.5 ± 1.90 (14)		79.3 ± 1.53 (14)	
WEEK 5	72.5 ± .966 (15)	70.2 ± .914 (14)		67.6 ± 1.11 (14)		69.6 ± 1.39 (14)	
WEEK 6	68.5 ± 1.01 (15)	65.9 ± .951 (14)		66.0 ± .853 (14)		68.8 ± 1.45 (14)	
WEEK 7	65.4 ± .949 (15)	63.6 ± 1.03 (14)		62.9 ± .925 (14)		71.3 ± 3.02 (14)	
WEEK 8	57.3 ± .553 (15)	59.3 ± .671 (14)		58.5 ± 1.38 (14)		67.7 ± 2.48 (14)	*
WEEK 9	55.9 ± .569 (15)	56.2 ± .723 (14)		54.8 ± 1.12 (14)		62.6 ± 1.15 (14)	*
WEEK 10	54.7 ± .695 (15)	54.5 ± .589 (14)		52.8 ± 1.04 (14)		56.7 ± 1.06 (14)	
WEEK 11	51.5 ± .512 (15)	51.0 ± .628 (14)		50.6 ± .809 (14)		57.1 ± 1.30 (14)	*
WEEK 12	52.1 ± .398 (15)	51.3 ± .736 (14)		50.2 ± 1.07 (14)		56.8 ± 2.10 (14)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 14 (continued)

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL	12.5 MG/KG	W	50 MG/KG	W	100 MG/KG	W
WEEK 13	48.8 + .347 (15)	48.8 + .650 (14)		48.5 + .652 (14)		65.5 + 1.07 (14)	*
WEEK 14	48.8 + .572 (15)	46.4 + .416 (14)		47.0 + .474 (14)		62.4 + 1.71 (14)	*
WEEK 15	50.6 + .437 (15)	48.0 + .539 (14)		48.4 + 1.00 (14)		59.5 + 1.16 (14)	*
WEEK 16	50.2 + .370 (15)	48.7 + .497 (14)		47.3 + .698 (14)		65.3 + 1.57 (14)	*
WEEK 17	49.0 + .371 (15)	48.4 + .747 (14)		48.4 + 1.07 (14)		66.3 + 1.44 (14)	*
WEEK 18	46.4 + .514 (15)	46.8 + .586 (14)		47.9 + .764 (14)		62.7 + 1.08 (14)	*
WEEK 19	47.0 + .423 (15)	46.9 + .682 (14)		49.2 + .966 (14)		62.6 + 1.80 (14)	*
WEEK 20	46.9 + .415 (15)	45.9 + .510 (14)		49.1 + .918 (14)		60.5 + 1.56 (14)	*
WEEK 21	47.9 + .366 (15)	47.1 + .643 (14)		52.0 + 1.24 (14)		65.3 + 1.71 (14)	*
WEEK 22	46.3 + .584 (15)	45.8 + .645 (14)		52.1 + 1.18 (14)		59.1 + 5.32 (14)	
WEEK 23	44.1 + .800 (15)	44.8 + 1.07 (14)		50.1 + 1.03 (14)		56.8 + 5.38 (14)	
WEEK 24	45.8 + .546 (15)	46.6 + .836 (14)		54.8 + 1.40 (14)		54.4 + 5.36 (14)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 15

EFFECTS OF EAP ON FOOD CONSUMPTION (G/KG (BODY WT) DAY) OF FEMALE RATS

DEPENDENT VARIABLE	TREATMENT GROUPS							
	CONTROL	12.5 MG/KG	W	50 MG/KG	W	200 MG/KG	W
WEEK 1	78.9 ± 2.77 (15)	85.2 ± .806 (14)		79.8 ± 1.53 (14)		52.4 ± 1.79 (14)	*
WEEK 2	77.1 ± 3.92 (15)	67.3 ± 2.11 (14)		67.8 ± 2.67 (14)		75.7 ± 1.85 (14)	
WEEK 3	79.5 ± 2.26 (15)	81.9 ± 1.65 (14)		80.1 ± 1.38 (14)		72.2 ± 1.13 (14)	
WEEK 4	81.9 ± 1.47 (15)	79.7 ± 1.11 (14)		77.4 ± 1.92 (14)		74.7 ± 1.40 (14)	
WEEK 5	79.3 ± 1.49 (15)	80.1 ± 1.33 (14)		71.2 ± .907 (14)	*	69.4 ± 1.26 (14)	*
WEEK 6	73.8 ± 1.51 (15)	71.5 ± 1.20 (14)		69.9 ± 1.54 (14)		66.8 ± 1.14 (14)	
WEEK 7	71.5 ± 1.19 (15)	68.3 ± 1.36 (14)		64.3 ± 1.11 (14)	*	65.7 ± 1.01 (14)	
WEEK 8	59.9 ± 1.15 (15)	62.9 ± .978 (14)		60.6 ± .926 (14)		62.1 ± .772 (14)	
WEEK 9	64.7 ± 1.43 (15)	63.8 ± .965 (13)		61.7 ± .810 (14)		63.3 ± 1.19 (14)	
WEEK 10	58.7 ± .824 (15)	61.5 ± 1.07 (14)		58.6 ± 1.12 (14)		60.1 ± 1.33 (14)	
WEEK 11	54.5 ± 1.06 (15)	57.2 ± .675 (14)		56.1 ± .617 (14)		65.0 ± 1.32 (14)	*
WEEK 12	57.9 ± 1.28 (15)	57.0 ± .922 (14)		55.2 ± 1.13 (14)		61.7 ± 1.59 (14)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W - WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 15 (continued)

DEPENDENT VARIABLE	TREATMENT GROUPS							
	CONTROL	12.5 MG/KG	W	50 MG/KG	W	100 MG/KG	W
WEEK 13	55.7 + .668 (15)	54.1 + 1.21 (14)		55.3 + .849 (14)		64.2 + 1.90 (14)	*
WEEK 14	50.9 + .457 (15)	50.6 + .741 (14)		54.0 + .804 (14)		55.2 + 1.77 (14)	
WEEK 15	62.5 + 1.47 (15)	55.8 + 1.27 (14)		54.2 + .785 (14)		57.0 + 1.96 (14)	
WEEK 16	55.5 + .590 (15)	55.5 + .865 (14)		53.8 + .684 (14)		59.3 + 1.87 (14)	
WEEK 17	53.0 + 1.04 (15)	55.5 + 1.53 (14)		53.0 + .524 (14)		55.3 + 1.80 (14)	
WEEK 18	55.0 + .898 (15)	53.6 + .977 (14)		53.1 + .893 (14)		53.1 + 2.41 (14)	
WEEK 19	52.8 + .744 (15)	53.0 + .985 (14)		52.9 + .823 (14)		54.0 + 1.78 (14)	
WEEK 20	53.9 + .982 (15)	51.6 + .907 (14)		51.4 + 1.02 (14)		50.9 + 1.72 (14)	
WEEK 21	52.8 + .542 (15)	51.7 + 1.14 (14)		51.0 + .549 (14)		54.1 + 2.05 (14)	
WEEK 22	50.3 + .500 (15)	51.6 + .882 (14)		52.6 + .846 (14)		53.0 + 1.81 (14)	
WEEK 23	48.8 + .736 (15)	49.4 + 1.47 (14)		49.8 + .910 (14)		51.5 + 2.19 (14)	
WEEK 24	47.1 + .644 (15)	47.4 + 1.03 (14)		48.4 + 1.02 (12)		53.0 + 1.67 (14)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 16

EFFECTS OF LAP ON FOOD CONSUMPTION (G/DAY)
OF MALE RATS

DEPENDENT VARIABLE	TREATMENT GROUPS					
	CONTROL	12.5 MG/KG	W	50 MG/KG	W	200 MG/KG	W
WEEK 1	12.9 ± .171 (15)	12.6 ± .215 (14)		11.1 ± .216 (14)	*	5.5 ± .189 (14)	*
WEEK 2	13.9 ± .127 (15)	12.8 ± .319 (14)		11.8 ± .401 (14)	*	10.0 ± .269 (14)	*
WEEK 3	15.9 ± .135 (15)	15.8 ± .134 (14)		14.4 ± .131 (14)	*	10.7 ± .139 (14)	*
WEEK 4	17.8 ± .383 (15)	16.6 ± .298 (14)		16.0 ± .409 (14)		12.7 ± .270 (14)	*
WEEK 5	18.1 ± .243 (15)	17.1 ± .195 (14)		15.3 ± .228 (14)	*	12.2 ± .247 (14)	*
WEEK 6	18.1 ± .250 (15)	17.0 ± .196 (14)		15.6 ± .204 (14)	*	13.0 ± .276 (14)	*
WEEK 7	17.9 ± .230 (15)	17.3 ± .283 (14)		15.7 ± .240 (14)	*	14.1 ± .498 (14)	*
WEEK 8	16.5 ± .158 (15)	16.6 ± .197 (14)		15.1 ± .421 (14)		13.9 ± .492 (14)	*
WEEK 9	16.7 ± .135 (15)	16.4 ± .210 (14)		14.6 ± .219 (14)	*	13.3 ± .269 (13)	*
WEEK 10	16.9 ± .155 (15)	16.5 ± .181 (14)		14.5 ± .296 (14)	*	12.4 ± .268 (14)	*
WEEK 11	16.3 ± .138 (15)	15.8 ± .182 (14)		14.3 ± .193 (14)	*	12.8 ± .323 (14)	*
WEEK 12	17.0 ± .111 (15)	16.3 ± .211 (14)		14.5 ± .271 (14)	*	12.9 ± .459 (14)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 16 (continued)

DEPENDENT VARIABLE	TREATMENT GROUPS					
	CONTROL	12.5 MG/KG	W	50 MG/KG	W	100 MG/KG	W
WEEK 13	16.3 + .114 (15)	15.9 + .203 (14)		14.4 + .181 (14)	*	15.9 + .285 (14)	*
WEEK 14	16.7 + .213 (15)	15.4 + .118 (14)		14.2 + .142 (14)	*	15.8 + .428 (14)	*
WEEK 15	17.5 + .141 (15)	16.2 + .162 (14)	*	14.8 + .265 (14)	*	15.5 + .390 (14)	*
WEEK 16	17.6 + .097 (15)	16.6 + .157 (14)		14.7 + .223 (14)	*	17.3 + .319 (14)	*
WEEK 17	17.5 + .094 (15)	16.8 + .279 (14)		15.1 + .267 (14)		18.1 + .342 (14)	
WEEK 18	16.8 + .167 (15)	16.4 + .176 (14)		15.1 + .218 (14)		17.5 + .336 (14)	
WEEK 19	17.3 + .136 (15)	16.8 + .244 (14)		15.8 + .253 (14)		17.8 + .493 (14)	
WEEK 20	17.6 + .132 (15)	16.7 + .175 (14)		16.0 + .277 (14)		17.6 + .330 (14)	
WEEK 21	18.2 + .085 (15)	17.3 + .214 (14)		17.1 + .365 (14)		19.4 + .475 (14)	
WEEK 22	17.8 + .179 (15)	17.1 + .241 (14)		17.3 + .354 (14)		17.8 + 1.53 (14)	
WEEK 23	17.0 + .314 (15)	16.7 + .423 (14)		16.5 + .316 (14)		17.1 + 1.58 (14)	
WEEK 24	17.8 + .162 (15)	17.6 + .287 (14)		18.3 + .412 (14)		16.7 + 1.62 (14)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 17

EFFECTS OF LAP ON FOOD CONSUMPTION (G/DAY)
OF FEMALE RATS

DEPENDENT VARIABLE	TREATMENT GROUPS					
	CONTROL	12.5 MG/KG	W	50 MG/KG	W	200 MG/KG	W
WEEK 1	8.4 ± .389 (15)	9.3 ± .109 (14)		8.3 ± .146 (14)		4.5 ± .161 (14)	*
WEEK 2	9.4 ± .546 (15)	7.9 ± .329 (14)		7.6 ± .387 (14)		7.1 ± .232 (14)	*
WEEK 3	10.7 ± .214 (15)	10.8 ± .224 (14)		10.1 ± .152 (14)		7.4 ± .066 (14)	*
WEEK 4	11.9 ± .289 (15)	11.3 ± .116 (14)		10.3 ± .232 (14)	*	8.3 ± .132 (14)	*
WEEK 5	12.2 ± .259 (15)	12.0 ± .214 (14)		10.0 ± .128 (14)	*	8.2 ± .186 (14)	*
WEEK 6	11.8 ± .243 (15)	11.1 ± .136 (14)		10.2 ± .218 (14)	*	8.3 ± .139 (14)	*
WEEK 7	11.7 ± .187 (15)	11.0 ± .185 (14)		9.7 ± .160 (14)	*	8.6 ± .131 (14)	*
WEEK 8	10.2 ± .184 (15)	10.4 ± .128 (14)		9.3 ± .141 (14)	*	8.4 ± .124 (14)	*
WEEK 9	11.4 ± .180 (15)	10.7 ± .177 (13)		9.6 ± .094 (14)	*	8.9 ± .175 (14)	*
WEEK 10	10.6 ± .133 (15)	10.7 ± .157 (14)		9.4 ± .161 (14)	*	8.9 ± .220 (14)	*
WEEK 11	10.0 ± .192 (15)	10.0 ± .092 (14)		9.1 ± .103 (14)		10.0 ± .232 (14)	
WEEK 12	10.7 ± .201 (15)	10.1 ± .118 (14)		9.1 ± .146 (14)	*	9.8 ± .302 (14)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 17 (continued)

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL	12.5 MG/KG	W	50 MG/KG	W	100 MG/KG	W
WEEK 13	10.4 + .121 (15)	9.7 + .184 (14)		9.3 + .083 (14)		11.2 + .177 (14)	
WEEK 14	9.6 + .124 (15)	9.2 + .118 (14)		9.2 + .119 (14)		9.9 + .186 (14)	
WEEK 15	11.9 + .266 (15)	10.3 + .176 (14)	*	9.2 + .080 (14)	*	10.7 + .171 (14)	*
WEEK 16	10.7 + .122 (15)	10.3 + .128 (14)		9.3 + .120 (14)		11.3 + .204 (14)	
WEEK 17	10.3 + .214 (15)	10.4 + .262 (14)		9.3 + .060 (14)		10.8 + .191 (14)	
WEEK 18	10.8 + .183 (15)	10.0 + .153 (14)		9.3 + .139 (14)		10.6 + .295 (14)	
WEEK 19	10.5 + .178 (15)	10.1 + .155 (14)		9.4 + .124 (14)		11.0 + .202 (14)	
WEEK 20	10.8 + .207 (15)	10.0 + .115 (14)		9.2 + .158 (14)		10.7 + .189 (14)	
WEEK 21	10.7 + .146 (15)	10.1 + .176 (14)		9.1 + .100 (14)		11.5 + .258 (14)	
WEEK 22	10.2 + .085 (15)	10.1 + .190 (14)		9.5 + .163 (14)		11.5 + .204 (14)	*
WEEK 23	9.9 + .186 (15)	9.6 + .249 (14)		9.0 + .126 (14)		11.2 + .274 (14)	*
WEEK 24	9.5 + .144 (15)	9.3 + .193 (14)		8.9 + .156 (12)		11.9 + .171 (14)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 18

EFFECTS OF LAP ON BODY WEIGHTS (G)
OF MALE RATS

DEPENDENT VARIABLE	B C	TREATMENT GROUPS: CONTROL GROUP	12.5 MG/KG IN DIET	T	R	50 MG/KG IN DIET	T	R	200 MG/KG IN DIET	T	R
INITIAL		120.48 ± 1.09 (75)	118.49 ± 1.07 (70)			117.54 ± 1.03 (70)			115.91 ± .983 (70)		A
WEEK 1		150.48 ± 1.41 (75)	147.64 ± 1.27 (70)			138.27 ± 1.26 (70)	+		106.84 ± 1.28 (70)	+	B
WEEK 2		181.29 ± 1.44 (75)	174.14 ± 1.57 (70)	+		160.96 ± 1.78 (70)	+		124.81 ± 1.41 (70)	+	B
WEEK 3		212.48 ± 1.44 (75)	206.20 ± 1.36 (70)	*		189.93 ± 1.42 (70)	+		142.99 ± 1.41 (70)	+	B
WEEK 4		231.91 ± 1.46 (75)	226.87 ± 1.41 (70)			210.13 ± 1.33 (70)	+		160.26 ± 1.55 (70)	+	B
WEEK 5		249.52 ± 1.60 (75)	245.04 ± 1.46 (70)			226.71 ± 1.38 (70)	+		175.43 ± 1.59 (70)	+	B
WEEK 6		264.37 ± 1.73 (75)	258.57 ± 1.64 (70)			237.89 ± 1.41 (70)	+		189.47 ± 1.59 (70)	+	B
WEEK 7		274.16 ± 1.79 (75)	273.46 ± 1.71 (70)			250.53 ± 1.54 (70)	+		198.87 ± 1.65 (70)	+	B
WEEK 8		288.88 ± 1.85 (75)	281.76 ± 1.90 (70)	*		258.83 ± 1.54 (70)	+		205.94 ± 1.55 (69)	+	B
WEEK 9		299.65 ± 1.91 (75)	293.44 ± 1.94 (70)			268.23 ± 1.61 (70)	+		212.42 ± 1.80 (69)	+	B
WEEK 10		309.64 ± 1.94 (75)	304.63 ± 1.88 (70)			276.67 ± 1.64 (70)	+		219.75 ± 1.85 (65)	+	B
WEEK 11		317.28 ± 1.98 (75)	311.40 ± 2.00 (70)			284.19 ± 1.75 (70)	+		221.70 ± 2.36 (64)	+	B
WEEK 12		326.80 ± 2.04 (75)	319.04 ± 2.05 (70)			290.50 ± 1.85 (70)	+		228.46 ± 2.51 (63)	+	B

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % = A,
20 % = B, 35 % = C, 50 % = D, RATIO TEST CANNOT BE CALCULATED = x .

TABLE 18 (continued)

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL GROUP	12.5 MG/KG IN DIET	T	R	50 MG/KG IN DIET	T	R	100 MG/KG IN DIET	T	R
WEEK 13	334.05 + 2.09 (75)	326.97 + 2.17 (70)	*		298.31 + 1.93 (70)	+		243.13 + 3.02 (63)	+	B
WEEK 14	341.19 + 2.14 (75)	334.36 + 2.15 (70)	*		303.09 + 1.94 (70)	+		253.29 + 3.17 (63)	+	B
WEEK 15	346.11 + 2.17 (75)	339.87 + 2.24 (70)	*		306.21 + 2.09 (70)	+		263.25 + 3.74 (61)	+	B
WEEK 16	351.25 + 2.19 (75)	342.67 + 2.29 (70)	+		311.63 + 2.13 (70)	+		267.43 + 3.73 (61)	+	B
WEEK 17	358.08 + 2.23 (75)	348.87 + 2.31 (70)	+		315.26 + 2.24 (70)	+	A	276.63 + 3.88 (59)	+	B
WEEK 18	363.16 + 2.28 (75)	353.26 + 2.40 (70)	+		318.04 + 2.39 (70)	+	A	283.12 + 4.06 (59)	+	A
WEEK 19	368.87 + 2.39 (75)	360.07 + 2.45 (70)	*		323.74 + 2.47 (70)	+	A	287.68 + 4.84 (57)	+	A
WEEK 20	374.77 + 2.43 (75)	365.30 + 2.50 (70)	+		327.99 + 2.55 (70)	+	A	298.06 + 5.20 (52)	+	A
WEEK 21	379.81 + 2.44 (75)	369.23 + 2.57 (70)	+		330.46 + 2.79 (70)	+	A	303.90 + 5.40 (50)	+	A
WEEK 22	383.77 + 2.48 (75)	374.63 + 2.62 (70)	*		334.01 + 2.90 (70)	+	A	308.69 + 5.51 (48)	+	A
WEEK 23	384.77 + 2.53 (75)	374.00 + 2.66 (70)	+		332.44 + 3.08 (70)	+	A	309.49 + 5.68 (47)	+	A
WEEK 24	389.25 + 2.46 (75)	379.51 + 2.76 (70)	+		336.33 + 3.24 (70)	+	A	314.37 + 6.27 (43)	+	A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X .

TABLE 19

EFFECTS OF LAP ON BODY WEIGHTS (G)
OF FEMALE RATS

DEPENDENT VARIABLE	B C	TREATMENT GROUPS: CONTROL GROUP	12.5 MG/KG IN DIET	T	R	50 MG/KG IN DIET	T	R	200 MG/KG IN DIET	T	R
INITIAL		94.27 ± .750 (75)	93.59 ± .731 (70)			93.24 ± .706 (70)			92.39 ± .639 (70)		
WEEK 1	*	105.17 ± 1.14 (75)	109.14 ± .852 (70)	*		103.74 ± .777 (70)			85.34 ± .633 (70)	*	A
WEEK 2	*	120.29 ± 1.44 (75)	116.83 ± 1.15 (70)			111.56 ± 1.16 (70)	*		93.64 ± .869 (70)	*	A
WEEK 3		133.92 ± .926 (75)	131.86 ± .817 (70)			125.90 ± .778 (70)	*		102.24 ± .757 (70)	*	B
WEEK 4		144.16 ± .860 (75)	141.44 ± .842 (70)			132.61 ± .750 (70)	*		110.11 ± .770 (70)	*	B
WEEK 5		152.84 ± .883 (75)	148.90 ± .931 (70)	*		139.66 ± .888 (70)	*		117.51 ± .817 (70)	*	B
WEEK 6		158.64 ± 1.03 (75)	154.46 ± .994 (70)	*		144.31 ± .886 (70)	*		123.63 ± .875 (70)	*	B
WEEK 7		161.92 ± .944 (74)	160.64 ± 1.01 (70)			149.49 ± .887 (70)	*		129.49 ± .946 (70)	*	A
WEEK 8		168.91 ± .979 (74)	164.31 ± 1.07 (70)	*		151.69 ± .909 (70)	*		134.30 ± 1.01 (70)	*	A
WEEK 9		174.45 ± 1.06 (74)	167.40 ± 1.02 (70)	*		155.16 ± .914 (70)	*		140.39 ± 1.18 (70)	*	A
WEEK 10		177.91 ± .966 (74)	172.04 ± 1.09 (70)	*		159.30 ± .928 (70)	*		146.61 ± 1.25 (70)	*	A
WEEK 11		181.11 ± 1.01 (74)	173.50 ± 1.09 (70)	*		161.36 ± .994 (70)	*		152.74 ± 1.34 (69)	*	A
WEEK 12	*	182.96 ± .991 (74)	176.20 ± 1.11 (70)	*		162.74 ± 1.00 (70)	*		157.70 ± 1.50 (69)	*	A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
** CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT CONTROL RATIO TEST . CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % A,
20 % B, 15 % C, 50 % D. RATIO TEST CANNOT BE CALCULATED = x .

TABLE 19 (continued)

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL GROUP	12.5 MG/KG IN DIET	T R	50 MG/KG IN DIET	T R	100 MG/KG IN DIET	T R
WEEK 13	186.77 + .986 (74)	178.97 + 1.07 (70)	+	167.44 + 1.02 (70)	+	166.72 + 1.39 (69)	+
WEEK 14	189.32 + 1.01 (74)	181.23 + 1.09 (70)	+	168.44 + 1.11 (70)	+	171.83 + 1.55 (69)	+
WEEK 15	190.74 + 1.03 (74)	183.67 + 1.09 (70)	+	168.99 + 1.17 (70)	+	179.43 + 1.60 (69)	+
WEEK 16	192.43 + 1.03 (74)	184.11 + 1.09 (70)	+	171.96 + 1.22 (70)	+	182.07 + 1.64 (69)	+
WEEK 17	195.14 + 1.00 (74)	186.37 + 1.09 (70)	+	175.63 + 1.21 (70)	+	185.58 + 1.61 (69)	+
WEEK 18	195.84 + .994 (74)	185.71 + 1.11 (70)	+	173.83 + 1.29 (70)	+	190.75 + 1.81 (69)	*
WEEK 19	198.31 + 1.03 (74)	190.01 + 1.11 (70)	+	176.00 + 1.23 (70)	+	193.87 + 1.91 (69)	*
WEEK 20	200.51 + 1.09 (74)	191.87 + 1.16 (70)	+	178.27 + 1.35 (70)	+	200.58 + 2.02 (69)	
WEEK 21	202.11 + 1.08 (74)	193.20 + 1.15 (70)	+	177.17 + 1.27 (70)	+ A	202.23 + 2.11 (69)	
WEEK 22	202.99 + 1.14 (74)	194.11 + 1.17 (70)	+	178.94 + 1.36 (70)	+ A	206.51 + 2.22 (69)	
WEEK 23	202.35 + 1.14 (74)	193.07 + 1.10 (70)	+	179.27 + 1.37 (70)	+	208.10 + 2.28 (69)	*
WEEK 24	202.99 + 1.15 (74)	194.59 + 1.15 (70)	+	181.06 + 1.38 (70)	+	214.13 + 2.95 (69)	+

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X .

TABLE 20

EFFECTS OF LAP ON DIFFERENCES IN BODY WEIGHTS (G) OF MALE RATS

DEPENDENT VARIABLE	B C	TREATMENT GROUPS: CONTROL GROUP	12.5 MG/KG IN DIET	T	R	50 MG/KG IN DIET	T	R	200 MG/KG IN DIET	T	R
WEEK 1	*	30.00 ± .603 (75)	29.16 ± .711 (70)			20.73 ± .655 (70)	+	B	-9.07 ± .929 (70)	+	D
WEEK 2	+	32.81 ± .615 (75)	26.50 ± 1.08 (70)	+	A	22.69 ± 1.37 (70)	+	B	17.97 ± .888 (70)	+	C
WEEK 3	+	29.19 ± .602 (75)	32.06 ± .636 (70)	+		28.97 ± .942 (70)			18.17 ± .569 (70)	+	B
WEEK 4		19.43 ± .378 (75)	20.67 ± .526 (70)			20.20 ± .516 (70)			17.27 ± .505 (70)	*	
WEEK 5		17.61 ± .399 (75)	18.17 ± .548 (70)			16.59 ± .428 (70)			15.17 ± .496 (70)	+	
WEEK 6	*	14.85 ± .357 (75)	13.53 ± .404 (70)	*		11.17 ± .324 (70)	+	A	14.04 ± .476 (70)		
WEEK 7	+	9.79 ± .431 (75)	14.89 ± .314 (70)	+	C	12.64 ± .449 (70)	+	A	9.40 ± .545 (70)		
WEEK 8	*	14.72 ± .374 (75)	8.30 ± .531 (70)	+	C	8.30 ± .406 (70)	+	C	7.20 ± .532 (69)	+	C
WEEK 9	+	10.77 ± .274 (75)	11.69 ± .513 (70)			9.40 ± .387 (70)	*		6.48 ± .780 (69)	+	B
WEEK 10	+	9.99 ± .356 (75)	11.19 ± .458 (70)	*		8.44 ± .362 (70)	*		5.82 ± .822 (65)	+	B
WEEK 11	+	7.64 ± .345 (75)	6.77 ± .420 (70)			7.51 ± .404 (70)			3.73 ± .921 (64)	+	B
WEEK 12	+	9.52 ± .373 (75)	7.64 ± .393 (70)	+		6.31 ± .468 (70)	+	B	4.52 ± .990 (63)	+	B

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % = A, 20 % = B, 35 % = C, 50 % = D. RATIO TEST CANNOT BE CALCULATED = x .

TABLE 20 (continued)

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL GROUP	12.5 MG/KG IN DIET	T R	50 MG/KG IN DIET	T R	100 MG/KG IN DIET	T R
WEEK 14	7.13 + .349 (75)	7.39 + .356 (70)		4.77 + .405 (70)	+ A	10.16 + 1.06 (63)	+
WEEK 15	4.92 + .325 (75)	5.51 + .323 (70)		3.13 + .513 (70)	+ A	9.54 + 1.23 (61)	+ C
WEEK 16	5.15 + .371 (75)	2.80 + .376 (70)	+ B	5.41 + .470 (70)		4.10 + 1.04 (61)	
WEEK 17	6.83 + .403 (75)	6.20 + .385 (70)		3.63 + .631 (70)	+ B	7.54 + .980 (59)	
WEEK 18	5.08 + .447 (75)	4.39 + .403 (70)		2.79 + .895 (70)	*	6.49 + 1.05 (59)	
WEEK 19	5.71 + .399 (75)	6.81 + .381 (70)	*	5.70 + .674 (70)		3.89 + 1.30 (57)	
WEEK 20	5.91 + .354 (75)	5.23 + .439 (70)		4.24 + .679 (70)	*	7.23 + 1.32 (52)	
WEEK 21	5.04 + .370 (75)	3.93 + .441 (70)		2.47 + .723 (70)	+ B	3.64 + .997 (50)	
WEEK 22	3.96 + .436 (75)	5.40 + .306 (70)	+	3.56 + .702 (70)		3.44 + 1.15 (48)	
WEEK 23	1.00 + .543 (75)	-.63 + .472 (70)	* X	-1.57 + .700 (70)	+ X	.45 + 1.52 (47)	X
WEEK 24	4.48 + .514 (75)	5.51 + .489 (70)		3.89 + .941 (70)		1.93 + 1.49 (43)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X .

TABLE 21

EFFECTS OF LAP ON DIFFERENCES IN BODY WEIGHTS (G)
OF FEMALE RATS

DEPENDENT VARIABLE	B C	TREATMENT GROUPS: CONTROL GROUP	12.5 MG/KG IN DIET	T	R	50 MG/KG IN DIET	T	R	200 MG/KG IN DIET	T	R
WEEK 1	+	10.91 ± .989 (75)	15.56 ± .397 (70)	+	A	10.50 ± .620 (70)			-7.04 ± .541 (70)	+	D
WEEK 2	+	15.12 ± 1.28 (75)	7.69 ± .989 (70)	+	B	7.81 ± .997 (70)	+	B	8.30 ± .722 (70)	+	B
WEEK 3	+	13.61 ± .952 (75)	15.03 ± .823 (70)			14.34 ± .795 (70)			8.60 ± .410 (70)	+	B
WEEK 4	+	10.24 ± .599 (75)	9.59 ± .313 (70)			6.71 ± .415 (70)	+	B	7.87 ± .374 (70)	+	A
WEEK 5		8.68 ± .360 (75)	7.46 ± .322 (70)			7.04 ± .392 (70)	*		7.40 ± .361 (70)		
WEEK 6	*	5.80 ± .363 (75)	5.56 ± .261 (70)			4.66 ± .288 (70)	*		6.11 ± .318 (70)		
WEEK 7		5.66 ± .316 (74)	6.19 ± .334 (70)	+	C	5.17 ± .326 (70)	*	A	5.86 ± .337 (70)	+	B
WEEK 8	*	6.99 ± .253 (74)	3.67 ± .248 (70)	+	C	2.20 ± .300 (70)	+	D	4.81 ± .364 (70)	+	A
WEEK 9	+	5.54 ± .282 (74)	3.09 ± .310 (70)	+	B	3.47 ± .287 (70)	+	B	6.09 ± .431 (70)		
WEEK 10	*	3.46 ± .306 (74)	4.64 ± .262 (70)	*		4.14 ± .302 (70)			6.23 ± .389 (70)	+	C
WEEK 11		3.20 ± .317 (74)	1.46 ± .308 (70)	+	B	2.06 ± .277 (70)		A	6.17 ± .351 (69)	+	D
WEEK 12	+	1.85 ± .321 (74)	2.70 ± .267 (70)	*		1.39 ± .243 (70)			4.96 ± .538 (69)	+	D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % = A,
20 % = B, 35 % = C, 50 % = D. RATIO TEST CANNOT BE CALCULATED = x .

TABLE 21 (continued)

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL GROUP	12.5 MG/KG IN DIET	T R	50 MG/KG IN DIET	T R	100 MG/KG IN DIET	T R
WEEK 14	2.55 + .355 (74)	2.26 + .288 (70)		1.00 + .343 (70)	+ B	5.10 + .594 (69)	+ B
WEEK 15	1.42 + .369 (74)	2.44 + .302 (70)	*	.54 + .309 (70)	A	7.61 + .491 (69)	+ D
WEEK 16	1.69 + .418 (74)	.44 + .300 (70)	* C	2.97 + .287 (70)	*	2.64 + .505 (69)	
WEEK 17	2.70 + .409 (74)	2.26 + .297 (70)		1.67 + .300 (70)	*	3.51 + .450 (69)	
WEEK 18	.70 + .381 (74)	-.66 + .315 (70)	+ X	.20 + .376 (70)	X	5.17 + .652 (69)	+ X
WEEK 19	2.47 + .434 (74)	4.30 + .269 (70)	+	2.17 + .326 (70)		3.12 + .669 (69)	
WEEK 20	2.20 + .390 (74)	1.86 + .326 (70)		2.27 + .358 (70)		6.71 + .592 (69)	+ D
WEEK 21	1.59 + .372 (74)	1.33 + .348 (70)		-1.10 + .393 (70)	+ D	1.65 + .607 (69)	
WEEK 22	.88 + .381 (74)	.91 + .364 (70)		1.77 + .307 (70)		4.28 + .596 (69)	+
WEEK 23	-.64 + .434 (74)	-1.04 + .397 (70)	X	.33 + .383 (70)	X	1.59 + .634 (69)	+ X
WEEK 24	.64 + .377 (74)	1.51 + .316 (70)	X	1.79 + .327 (70)	* X	6.03 + 1.44 (69)	+ X

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X .

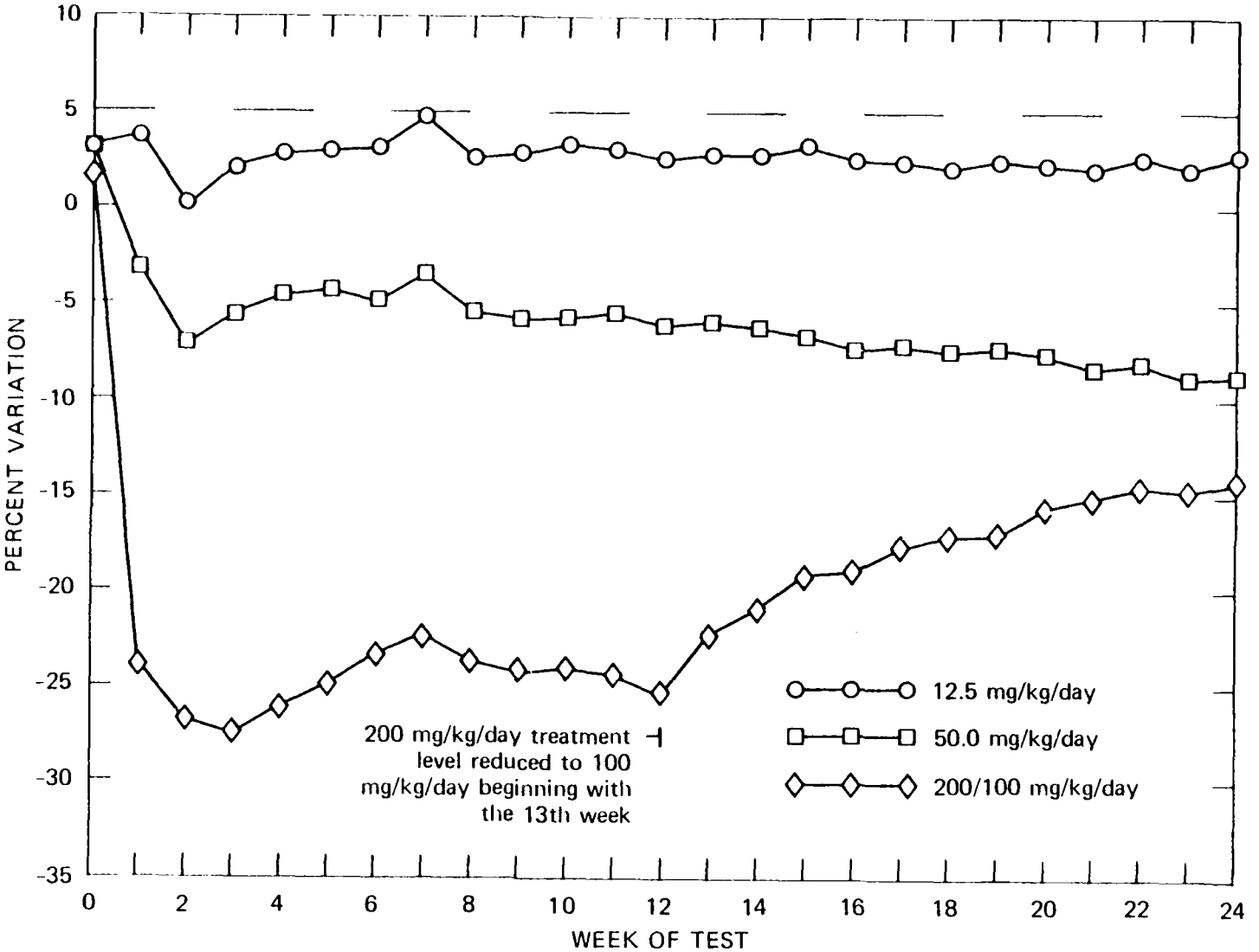


FIGURE 3 PERCENT BODY WEIGHT VARIATION FROM CONTROL MALES

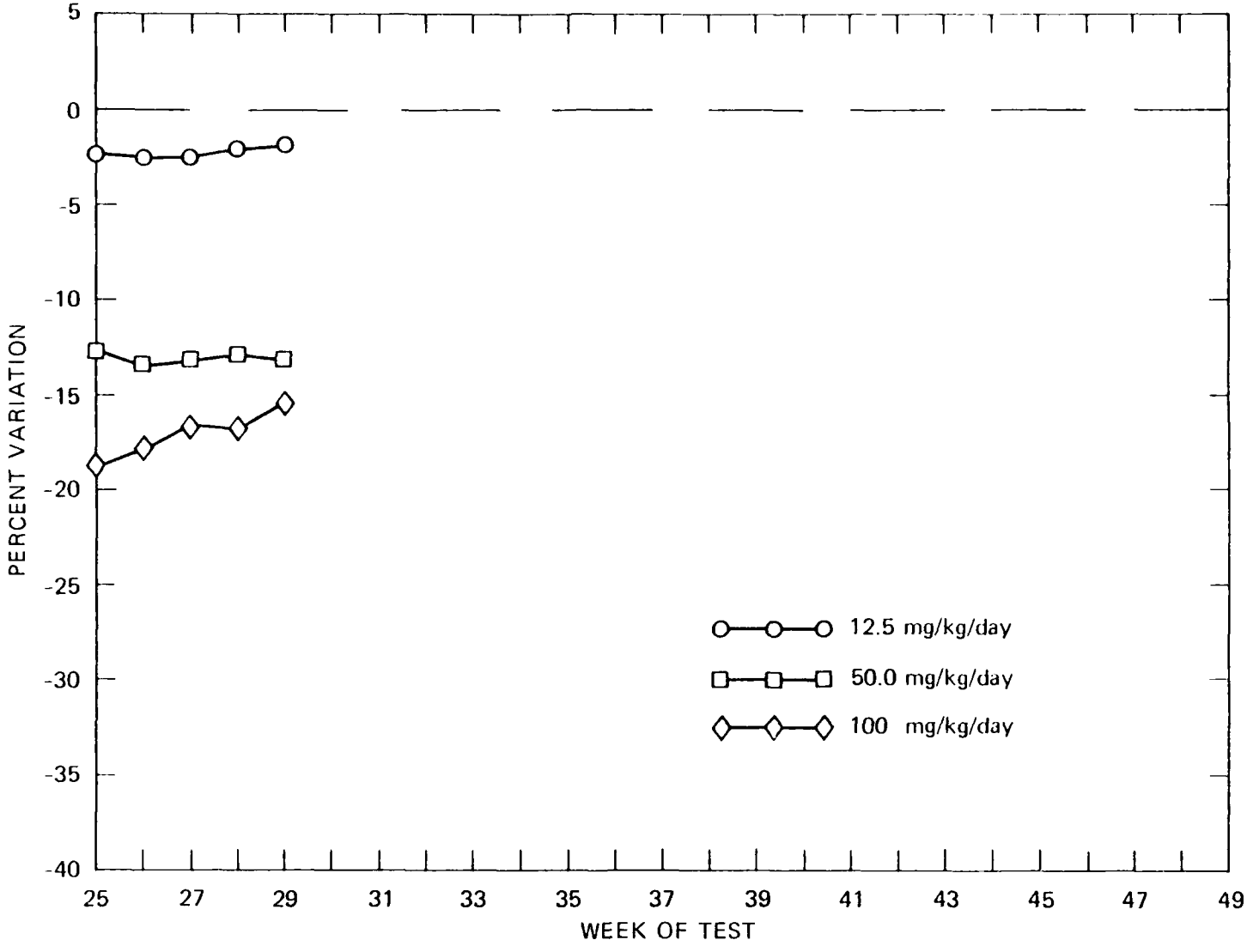


FIGURE 3 (Continued) PERCENT BODY WEIGHT VARIATION FROM CONTROL MALES

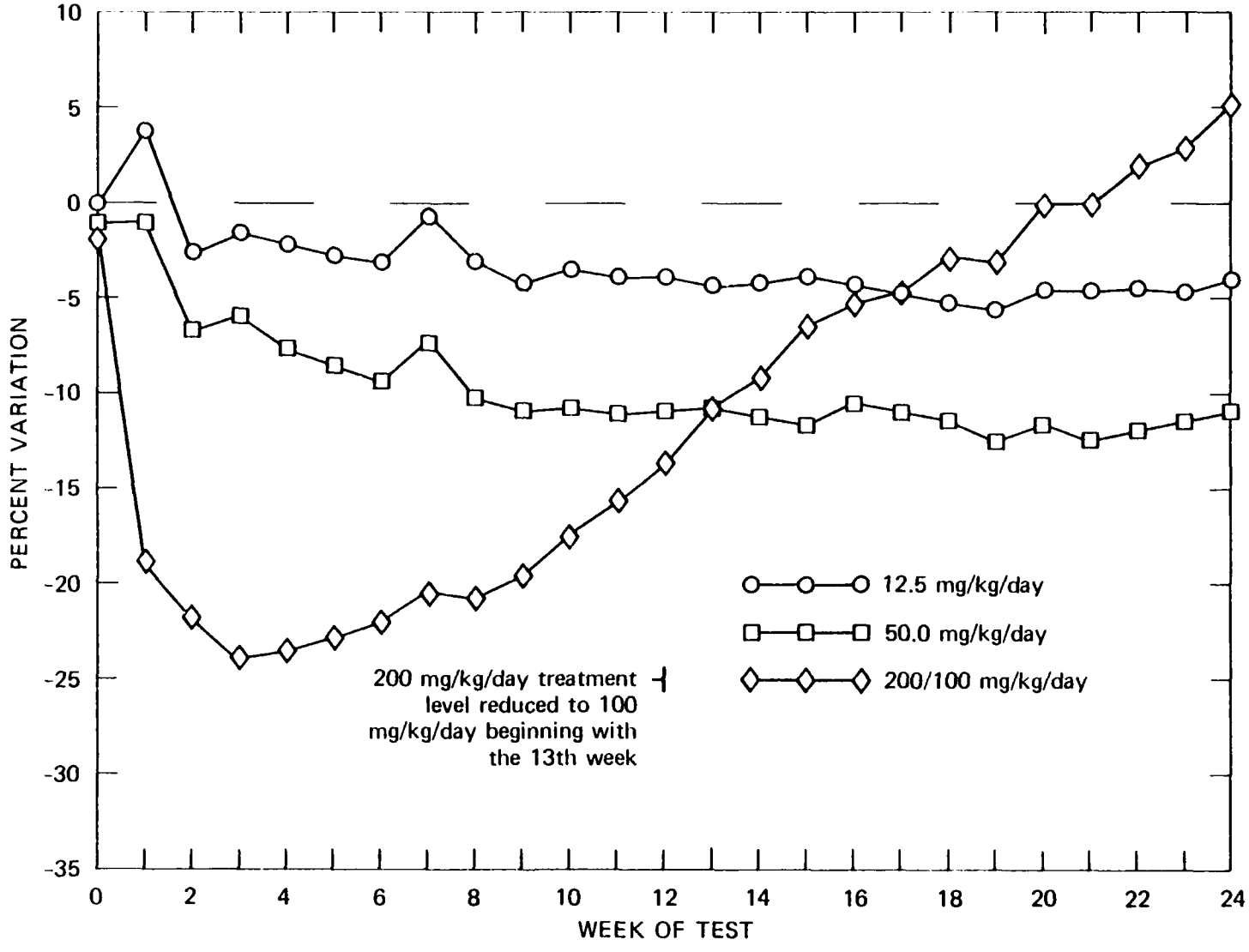


FIGURE 4 PERCENT BODY WEIGHT VARIATION FROM CONTROL FEMALES

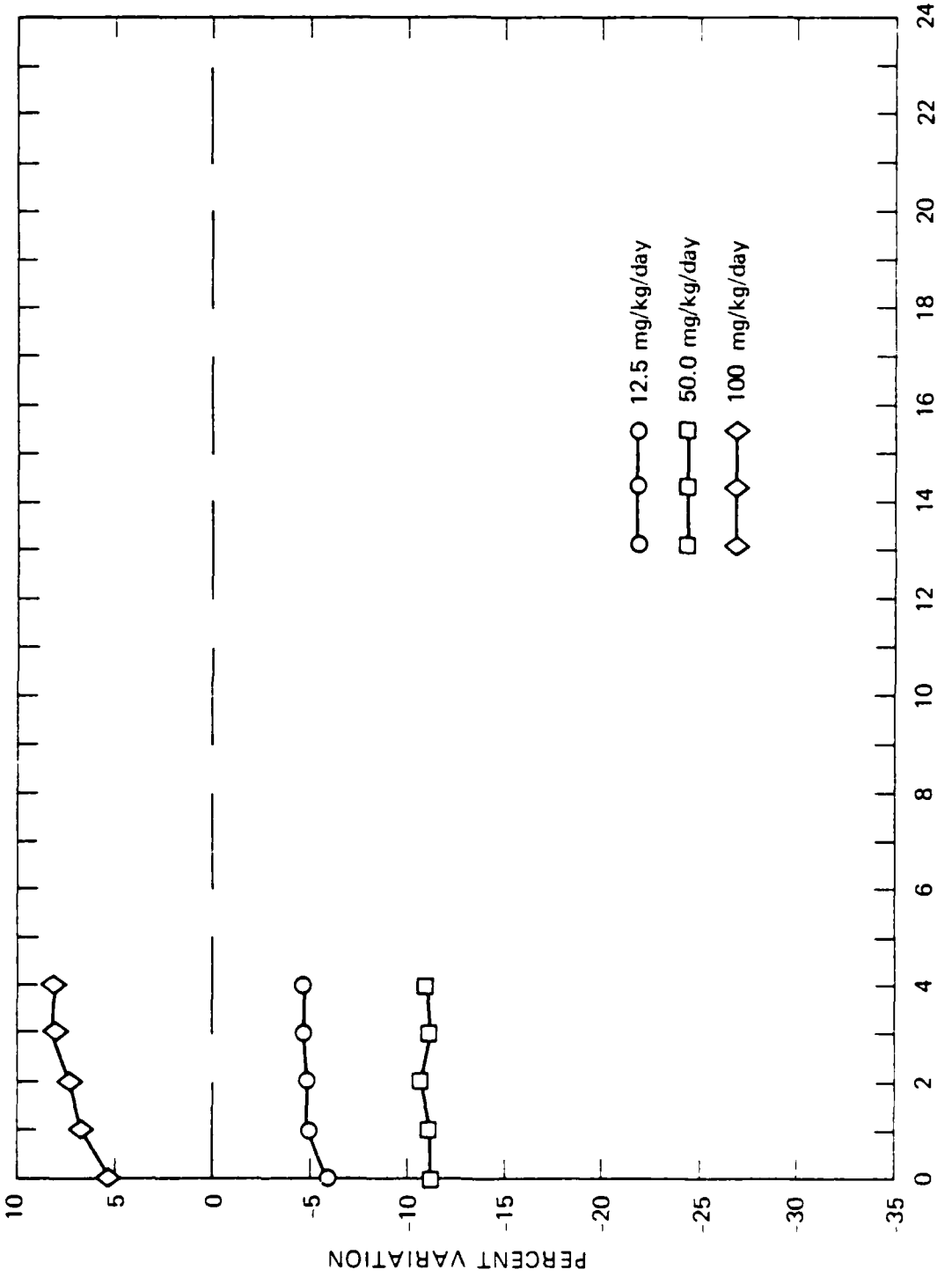


FIGURE 4 (Continued) PERCENT BODY WEIGHT VARIATION FROM CONTROL FEMALES

Attachment A

COMPUTER-GENERATED LD50 ANALYSES

--- LD50 ANALYSIS --- 80/05/21. 16.22.37.

PROJ 8816 LAP FISHER RAT ORAL LD50.
MALES

****** INPUT DATA ******

LEVEL NO.	DOSE	NUMBER EXPOSED	NUMBER DEAD	PERCENT MORTALITY
1	750.0	10	10	100.00
2	600.0	10	10	100.00
3	450.0	10	8	80.00
4	300.0	10	5	50.00
5	150.0	10	2	20.00

LEVEL NO.	BINOMIAL PROB-ABILITY
1	.0010+
2	.0010+
3	.0547+
4	.6230
5	.0547-

****** BINOMIAL METHOD ******

THE INTERVAL -INFINITY TO 600.0 IS
A 95 PERCENT CONFIDENCE INTERVAL FOR THE LD50
CALCULATED USING THE BINOMIAL METHOD.

USING LINEAR INTERPOLATION ON THE LOG DOSES,
A POINT ESTIMATE FOR THE LC50 IS 300.0

PROJ 8846 LAP FISHER RAT ORAL LD50.
MALES

80/05/21. 16.22.37.

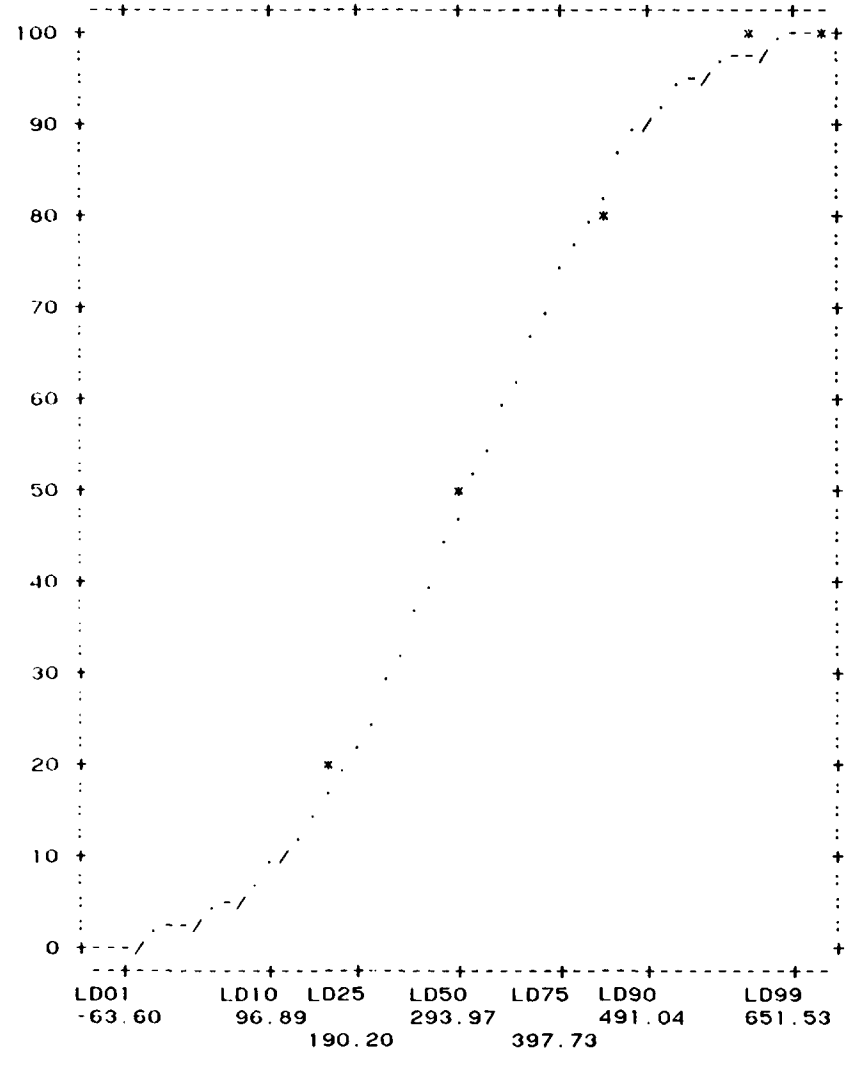
****** PROBIT METHOD ******

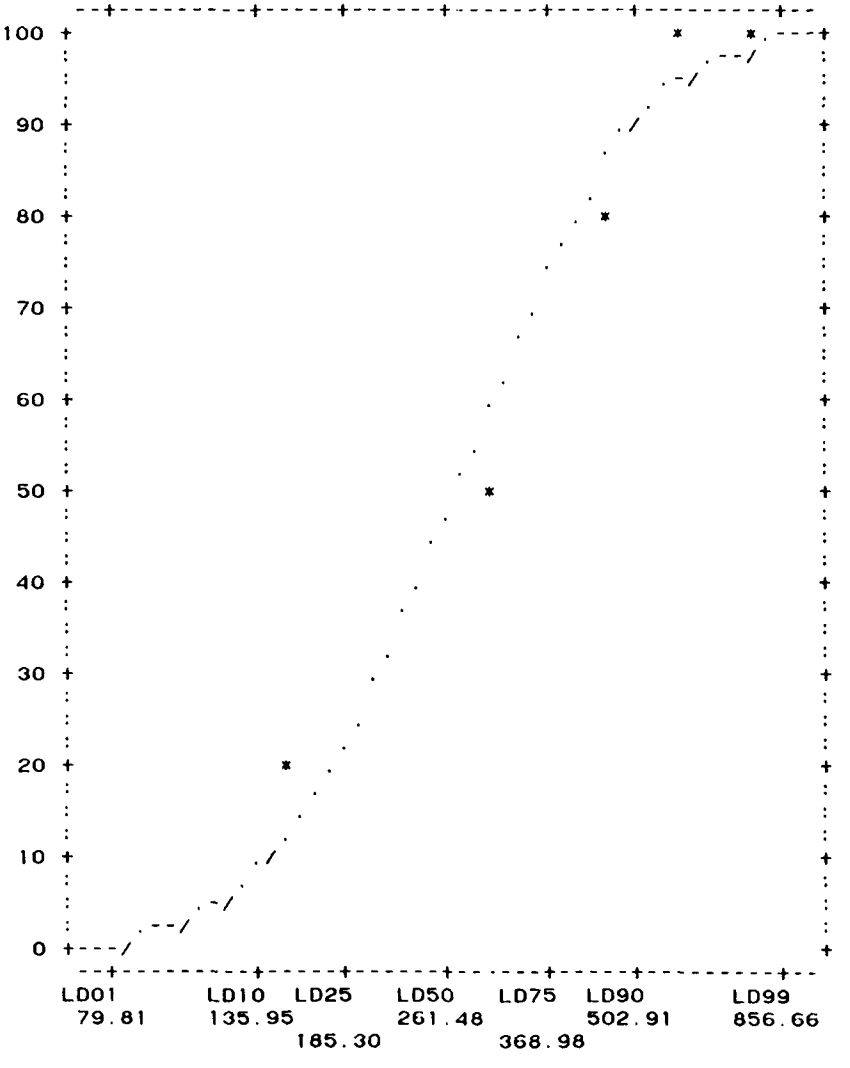
LINEAR DOSE MODEL

LOWER 95 PCT LIMIT	LD50 ESTIMATE	UPPER 95 PCT LIMIT
200.1	294.0	367.3

LOG DOSE MODEL

LOWER 95 PCT LIMIT	LD50 ESTIMATE	UPPER 95 PCT LIMIT
189.2	261.5	329.5





--- LD50 ANALYSIS --- 80/05/21. 16 22.37.

PROJ 8816 LAP FISHER RAT ORAL LD50.
MALES

****** MOVING AVERAGE METHOD ******

	LINEAR DOSE MODEL			LOG DOSE MODEL		
SPAN	LOWER 95 PCT LIMIT	LD50 ESTIMATE	UPPER 95 PCT LIMIT	LOWER 95 PCT LIMIT	LD50 ESTIMATE	UPPER 95 PCT LIMIT
3	181.2	300.0	377.8	-	-	-
2	158.6	300.0	441.4	166.3	279.2	468.5
1	-	300.0	-	-	300.0	-

****** TRIMMED SPEARMAN-KARBER METHOD ******

	LINEAR DOSE MODEL			LOG DOSE MODEL		
TRIM CONS.	LOWER 95 PCT LIMIT	LD50 ESTIMATE	UPPER 95 PCT LIMIT	LOWER 95 PCT LIMIT	LD50 ESTIMATE	UPPER 95 PCT LIMIT
.200	209.2	300.0	390.8	199.6	279.2	390.4

--- LD50 ANALYSIS --- 80/05/21 16 22 37.

PROJ 8816 LAP FISHER RAT ORAL LD50
FEMALES

****** INPUT DATA ******

(WARNING - VALIDITY OF RESULTS MAY BE SUSPECT,
SINCE NO DOSE RESULTED IN AN OBSERVED MORTALITY
RATE OF 35 PERCENT OR LESS.)

LEVEL NO.	DOSE	NUMBER EXPOSED	NUMBER DEAD	PERCENT MORTALITY
1	750.0	10	10	100.00
2	600.0	10	10	100.00
3	450.0	10	9	90.00
4	300.0	10	4	40.00
5	150.0	10	4	40.00

LEVEL NO.	BINOMIAL PROB-ABILITY
1	.0010+
2	.0010+
3	.0107+
4	.3770-
5	.3770-

****** BINOMIAL METHOD ******

THE INTERVAL -INFINITY TO 450.0 IS
A 95 PERCENT CONFIDENCE INTERVAL FOR THE LD50
CALCULATED USING THE BINOMIAL METHOD.

USING LINEAR INTERPOLATION ON THE LOG DOSES,
A POINT ESTIMATE FOR THE LC50 IS 325.3

-157.08 27.11 253.29 479.47 663.66 52.42 100.37 222.84 494.75 947.28
134.20 372.38 146.42 339.14

--- LD50 ANALYSIS --- 80/05/21. 16.22.37.

PROJ 8816 LAP FISHER RAT ORAL LD50.
FEMALES

****** MOVING AVERAGE METHOD ******

	LINEAR DOSE MODEL			LOG DOSE MODEL		
SPAN	LOWER 95 PCT LIMIT	LD50 ESTIMATE	UPPER 95 PCT LIMIT	LOWER 95 PCT LIMIT	LD50 ESTIMATE	UPPER 95 PCT LIMIT
2	9.604	279.7	444.8	96.39	259.2	474.5
1	15.94	327.3	392.8	139.2	323.0	385.5

****** TRIMMED SPEARMAN-KARBER METHOD ******

	LINEAR DOSE MODEL			LOG DOSE MODEL		
TRIM CONS.	LOWER 95 PCT LIMIT	LD50 ESTIMATE	UPPER 95 PCT LIMIT	LOWER 95 PCT LIMIT	LD50 ESTIMATE	UPPER 95 PCT LIMIT
.400	254.8	330.0	405.2	265.5	325.3	398.7

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